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=> d his

     (FILE 'HOME' ENTERED AT 19:30:11 ON 11 JUN 2003)

     FILE 'CAPLUS, USPATFULL' ENTERED AT 19:30:36 ON 11 JUN 2003
L1          3165 FILE CAPLUS
L2          1392 FILE USPATFULL
     TOTAL FOR ALL FILES
L3          4557 S (PDE OR PDR?) AND PHOSPHODIESTERASE
L4            12 FILE CAPLUS
L5           487 FILE USPATFULL
     TOTAL FOR ALL FILES
L6           499 S L3 AND (TREAT? (1S) (WOUND? OR ULCER? OR SORE? IR DECUBITUS))
L7            12 FILE CAPLUS
L8           489 FILE USPATFULL
     TOTAL FOR ALL FILES
L9           501 S L3 AND (TREAT? (1S) (WOUND? OR ULCER? OR SORE? OR DECUBITUS))
L10            0 FILE CAPLUS
L11           43 FILE USPATFULL
     TOTAL FOR ALL FILES
L12           43 S L9 AND L3/CLM
L13        91518 FILE CAPLUS
L14         9896 FILE USPATFULL
     TOTAL FOR ALL FILES
L15       101414 S (NITRIC OXIDE OR CGMP )
L16        91518 FILE CAPLUS
L17         9896 FILE USPATFULL
     TOTAL FOR ALL FILES
L18       101414 S L15
L19          224 FILE CAPLUS
L20         1843 FILE USPATFULL
     TOTAL FOR ALL FILES
L21         2067 S L18 AND (TREAT? (1S) (WOUND? OR ULCER? OR SORE? OR DECUBITUS)
L22          113 FILE CAPLUS
L23          167 FILE USPATFULL
     TOTAL FOR ALL FILES
L24          280 S L18 (1S) (TREAT? (1S) (WOUND? OR ULCER? OR SORE? OR DECUBITUS
L25           82 FILE CAPLUS
L26         1072 FILE USPATFULL
     TOTAL FOR ALL FILES
L27         1154 S L18 AND (TREAT? (1S) (WOUND? OR (VENOUS ULCER?) OR (ATERIAL U

     FILE 'CAPLUS, MEDLINE, SCISEARCH, EMBASE' ENTERED AT 19:52:21 ON 11 JUN
     2003
L28           82 FILE CAPLUS
L29           52 FILE MEDLINE
L30           88 FILE SCISEARCH
L31           73 FILE EMBASE
     TOTAL FOR ALL FILES
L32          295 S L27
L33            0 FILE CAPLUS
L34            0 FILE MEDLINE
L35            0 FILE SCISEARCH
L36            0 FILE EMBASE
     TOTAL FOR ALL FILES
L37            0 S L32 AND L3
L38            5 FILE CAPLUS
L39            0 FILE MEDLINE
L40            0 FILE SCISEARCH
L41            0 FILE EMBASE
     TOTAL FOR ALL FILES
L42            5 S L32 AND PHOSPHODIESTERASE?
```

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L43          465 FILE CAPLUS
L44          485 FILE MEDLINE
L45          426 FILE SCISEARCH
L46          364 FILE EMBASE
     TOTAL FOR ALL FILES
L47         1740 S L18 AND ( (WOUND? OR (VENOUS ULCER?) OR (ATERIAL ULCER?) OR S
L48            7 FILE CAPLUS
L49            4 FILE MEDLINE
L50            1 FILE SCISEARCH
L51            0 FILE EMBASE
     TOTAL FOR ALL FILES
L52           12 S L47 AND PHOSPHODIESTERASE?
L53            2 FILE CAPLUS
L54            4 FILE MEDLINE
L55            1 FILE SCISEARCH
L56            0 FILE EMBASE
     TOTAL FOR ALL FILES
L57            7 S L52 NOT L42
L58            6 DUP REM L57 (1 DUPLICATE REMOVED)
                 E CHRONIC ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJER?
                 E CHRONIC ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJUR?
L59            0 FILE CAPLUS
L60            0 FILE MEDLINE
L61            0 FILE SCISEARCH
L62            0 FILE EMBASE
     TOTAL FOR ALL FILES
L63            0 S CHRONIC ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJUR?
L64            0 FILE CAPLUS
L65            0 FILE MEDLINE
L66            0 FILE SCISEARCH
L67            0 FILE EMBASE
     TOTAL FOR ALL FILES
L68            0 S  ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJUR?
L69            0 FILE CAPLUS
L70            0 FILE MEDLINE
L71            0 FILE SCISEARCH
L72            0 FILE EMBASE
     TOTAL FOR ALL FILES
L73            0 S  ARTERIAL ULCER? AND  PERFUSION INJUR?
L74         4195 FILE CAPLUS
L75         9087 FILE MEDLINE
L76         6734 FILE SCISEARCH
L77        15975 FILE EMBASE
     TOTAL FOR ALL FILES
L78        35991 S DIPYRIDAMOLE OR ZAPRONIST OR SILDENAFIL
L79            6 FILE CAPLUS
L80           10 FILE MEDLINE
L81            7 FILE SCISEARCH
L82           31 FILE EMBASE
     TOTAL FOR ALL FILES
L83           54 S L78 (1S) (TREAT? (1S) (WOUND? OR ULCER? OR SORE? OR DECUBITUS
L84           38 DUP REM L83 (16 DUPLICATES REMOVED)
L85           39 FILE CAPLUS
L86           17 FILE MEDLINE
L87           16 FILE SCISEARCH
L88           24 FILE EMBASE
     TOTAL FOR ALL FILES
L89           96 S DIPYRIDAMOLE AND (PHOSPHODIESTERASE (3W) (5 OR V))

     FILE 'REGISTRY' ENTERED AT 20:26:35 ON 11 JUN 2003
L90            1 S DIPYRIDAMOLE/CN

     FILE 'CAPLUS' ENTERED AT 20:27:30 ON 11 JUN 2003
L91            1 S WO2002015893/PN
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L92         2415 S L90/BIOL
L93          210 S L92 AND (PHOSPHODIESTERASE)
L94           13 S L92 AND (PHOSPHODIESTERASE (2W) 5)
L95            0 S L94 AND (ULCER? OR WOUND?)
L96           22 S L92 AND (ULCER? OR WOUND?)
L97            3 S L96 AND (PHOSPHODIESTERASE)
L98           13 S L90 AND (PHOSPHODIESTERASE (2W) 5)
L99            5 S DIPYRIDAMOLE (1S) (PHOSPHODIESTERASE (2W) 5)
L100           0 S DIPYRIDAMOLE (1S) LEG ULCER?
L101           0 S DIPYRIDAMOLE (2S) (LEG ULCER?)

     FILE 'CAPLUS, MEDLINE, SCISEARCH, EMBASE' ENTERED AT 20:38:22 ON 11 JUN
     2003
L102           0 FILE CAPLUS
L103           1 FILE MEDLINE
L104           0 FILE SCISEARCH
L105           4 FILE EMBASE
     TOTAL FOR ALL FILES
L106           5 S DIPYRIDAMOLE (2S) (LEG ULCER?)

     FILE 'REGISTRY' ENTERED AT 20:45:03 ON 11 JUN 2003
L107           0 S ZAPRONIST/CN
L108           0 S ZAPRONIST
L109           1 S ZAPRINAST/CN

=> save l09927344/l
ENTER L#, L# RANGE, ALL, OR (END):all
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ENTER NAME OR (END):a09927344/l
L# LIST L106 HAS BEEN SAVED AS 'A09927344/L'
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L153 ANSWER 5 OF 6 USPATFULL

ACCESSION NUMBER:	2002:72919 USPATFULL
TITLE:	Formulations and methods of using nitric oxide mimetics against a malignant cell phenotype
INVENTOR(S):	Adams, Michael A., Kingston, CANADA Graham, Charles H., Kingston, CANADA Heaton, Jeremy P.W., Ganonoque, CANADA Postovit, Lynne-Marie, Kingston, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002040059	A1	20020404
APPLICATION INFO.:	US 2001-842547	A1	20010426 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-277469P	20010321 (60)
	US 2000-199757P	20000426 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	LICATA & TYRRELL P.C., 66 E. MAIN STREET, MARLTON, NJ, 08053
NUMBER OF CLAIMS:	32
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	4 Drawing Page(s)
LINE COUNT:	1488

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L153 ANSWER 5 OF 6 USPATFULL

DETD [0021] Accordingly, the present invention relates to the use of low dose nitric oxide mimetic therapy in inhibiting and preventing a malignant cell phenotype of cells. The methods and formulations of the present invention provide new therapeutic approaches for the treatment and prevention of cancer in animals. For purposes of the present invention, by "treatment" or "treating" it is meant to encompass all means for controlling cancer by reducing growth of cells exhibiting a malignant cell phenotype and improving response to antimalignant therapeutic modalities. Thus, by "treatment" or "treating" it is meant to inhibit the survival and/or growth of cells exhibiting a malignant cell phenotype, prevent the survival and/or growth of cells exhibiting a malignant cell phenotype, decrease the invasiveness of cells exhibiting a malignant cell phenotype, decrease the progression of cells exhibiting a malignant cell phenotype, decrease the metastases of cells exhibiting a malignant cell phenotype, increase the regression of cells exhibiting a malignant cell phenotype, and/or facilitate the killing of cells exhibiting a malignant cell phenotype. "Treatment" or "treating" is also meant to encompass maintenance of cells exhibiting a malignant cell phenotype in a dormant state at their primary site as well as secondary sites. Further, by "treating or "treatment" it is meant to increase the efficacy as well as prevent or decrease resistance to antimalignant therapeutic modalities. By "antimalignant therapeutic modalities" it is meant to include, but is not limited to, radiation therapies, thermal therapies, immunotherapies, chemotherapies, and other therapies used by those of skill in the art in the treatment of cancer and other malignancies. By "increasing the efficacy" it is meant to include an increase in potency and/or activity of the antimalignant therapeutic modality and/or a decrease in the development of resistance to the antimalignant therapeutic modality. The present invention also relates to methods of monitoring and/or diagnosing malignant cell phenotypes in an animal via measurement of tumor selective markers in an animal in the presence of low dose NO mimetic therapy. Exemplary tumor markers useful in the monitoring and diagnosing of tumor progression and metastases include, but are not limited to, prostate specific antigen (PSA) for prostate cancer, carcinoembryonic antigen (CEA) for gastrointestinal cancer, .alpha.-fetoprotein and .beta.HCG for testicular cancer, CA19-9 and CA72-4 for gastric cancer, CA15-3 for breast cancer and the cell surface receptors for estrogen and Her-2 for breast cancer. Additional markers which can be monitored for diagnostic purposes include, but are not limited to, Protein Regulated by OXYgen-1 (PROXY-1), also known as NDRG-1, plasminogen activator inhibitor (PAI-1), **urokinase** -type plasminogen activator receptor (uPAR) and vascular endothelial growth factor (VEGF). Further, as will be understood by those of skill in the art upon reading this disclosure, additional tumor markers to those exemplified herein can also be monitored in the present invention. In a preferred embodiment, the tumor marker is detectable in a biological fluid such a serum, plasma or urine. No change, a decrease or deceleration in the increase of the level of one or more of these markers in an animal following administration of a low dose nitric oxide mimetic as compared to the level of the marker in the animal prior to administration of the low dose nitric oxide mimetic is indicative of a malignant cell phenotype in the animal.

DETD [0030] In a preferred embodiment of the present invention, more than one NO mimetic is administered. In this embodiment, it is preferred that the NO mimetics target or act upon different parts of the NO pathway of the cell. For example, an NO donor can be co-administered with a compound that inhibits cyclic nucleotide (e.g. cAMP or cGMP) degradation such as a phosphodiesterase inhibitor. Preferred phosphodiesterase (PDE) inhibitors useful as NO mimetics are those inhibiting PDE-1 through **PDE-5**.

DETD [0034] For example, it has been shown that uPAR mRNA and cell surface uPAR protein levels increase under hypoxic conditions. uPAR is a high

affinity cell surface receptor for pro-**urokinase**-type plasminogen activator (pro-uPA). Upon binding of pro-uPA to uPAR, the inactive single-chain pro-uPA is cleaved into its active, two-chain form. The activated enzyme, still attached to the receptor, then acts to convert plasminogen into plasmin, which ultimately degrades several components of the extracellular matrix (ECM). Active uPA also serves to activate both latent metalloproteinases and growth factors. uPAR also serves as a receptor for the ECM molecule, vitronectin. In combination, these functions increase cellular invasion and potential for invasiveness. A positive correlation between hypoxia-induced uPAR up-regulation and carcinoma cell invasiveness has been suggested (Graham et al. Int. J. Cancer 1999 80:617-623). In addition, we have now shown hyponitroxia induced by administration of the nitric oxide synthase antagonist L-NMMA (0.5 mM) in hypoxic (1% O.sub.2) and nonhypoxic (5% and 20% O.sub.2) conditions to increase uPAR mRNA levels in human MDA-MD-231 cells incubated for 24 hours at 37.degree..

DETD [0054] Low dose formulations of nitric oxide mimetics which ultimately result in an increase, restoration or maintenance of nitric oxide mimetic activity of cells sufficient to prevent or inhibit a malignant cell phenotype can be produced in accordance with formulation methods known in the art. Formulations for the administration of nitric oxide mimetics in accordance with the method of the present invention can take the form of ointments, transdermal patches, transbuccal patches, injectables, nasal inhalant forms, spray forms for deep lung delivery through the mouth, orally administered ingestible tablets and capsules, and tablets or lozenges, or "lollipop" formulations for administration through the oral mucosal tissue. The latter formulations included tablets, lozenges and the like which are dissolved while being held on or under the tongue, or in the buccal pouch. It is preferred that the pharmaceutical preparations provide a low dose of the nitric oxide mimetic sufficient to increase, restore or maintain nitric oxide mimetic activity at a level which inhibits or prevents a malignant cell phenotype, also referred to herein as a therapeutically effective amount, during the period in which cellular nitric oxide mimetic activity of cells is lowered. Also preferred are formulations comprising more than one NO mimetic. In this embodiment, it is preferred that the NO mimetics target or act on different parts of the NO pathway. For example, an NO donor can be co-administered with a compound that inhibits cyclic nucleotide (e.g. cAMP or cGMP) degradation such as a phosphodiesterase inhibitor. Preferred phosphodiesterase (PDE) inhibitors useful as NO mimetics are those inhibiting PDE-1 through **PDE-5**.

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      (FILE 'HOME' ENTERED AT 19:30:11 ON 11 JUN 2003)

      FILE 'CAPLUS, USPATFULL' ENTERED AT 19:30:36 ON 11 JUN 2003
L1          3165 FILE CAPLUS
L2          1392 FILE USPATFULL
      TOTAL FOR ALL FILES
L3          4557 S (PDE OR PDR?) AND PHOSPHODIESTERASE
L4            12 FILE CAPLUS
L5           487 FILE USPATFULL
      TOTAL FOR ALL FILES
L6           499 S L3 AND (TREAT? (1S) (WOUND? OR ULCER? OR SORE? IR DECUBITUS))
L7            12 FILE CAPLUS
L8           489 FILE USPATFULL
      TOTAL FOR ALL FILES
L9           501 S L3 AND (TREAT? (1S) (WOUND? OR ULCER? OR SORE? OR DECUBITUS))
L10            0 FILE CAPLUS
L11           43 FILE USPATFULL
      TOTAL FOR ALL FILES
L12           43 S L9 AND L3/CLM
L13        91518 FILE CAPLUS
L14         9896 FILE USPATFULL
      TOTAL FOR ALL FILES
L15       101414 S (NITRIC OXIDE OR CGMP )
L16        91518 FILE CAPLUS
L17         9896 FILE USPATFULL
      TOTAL FOR ALL FILES
L18       101414 S L15
L19           224 FILE CAPLUS
L20          1843 FILE USPATFULL
      TOTAL FOR ALL FILES
L21          2067 S L18 AND (TREAT? (1S) (WOUND? OR ULCER? OR SORE? OR DECUBITUS)
L22           113 FILE CAPLUS
L23           167 FILE USPATFULL
      TOTAL FOR ALL FILES
L24           280 S L18 (1S) (TREAT? (1S) (WOUND? OR ULCER? OR SORE? OR DECUBITUS
L25            82 FILE CAPLUS
L26          1072 FILE USPATFULL
      TOTAL FOR ALL FILES
L27          1154 S L18 AND (TREAT? (1S) (WOUND? OR (VENOUS ULCER?) OR (ATERIAL U

      FILE 'CAPLUS, MEDLINE, SCISEARCH, EMBASE' ENTERED AT 19:52:21 ON 11 JUN
      2003
L28            82 FILE CAPLUS
L29            52 FILE MEDLINE
L30            88 FILE SCISEARCH
L31            73 FILE EMBASE
      TOTAL FOR ALL FILES
L32           295 S L27
L33             0 FILE CAPLUS
L34             0 FILE MEDLINE
L35             0 FILE SCISEARCH
L36             0 FILE EMBASE
      TOTAL FOR ALL FILES
L37             0 S L32 AND L3
L38             5 FILE CAPLUS
L39             0 FILE MEDLINE
L40             0 FILE SCISEARCH
L41             0 FILE EMBASE
      TOTAL FOR ALL FILES
L42             5 S L32 AND PHOSPHODIESTERASE?
L43           465 FILE CAPLUS
L44           485 FILE MEDLINE
L45           426 FILE SCISEARCH
L46           364 FILE EMBASE
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     TOTAL FOR ALL FILES
L47         1740 S L18 AND ( (WOUND? OR (VENOUS ULCER?) OR (ATERIAL ULCER?) OR S
L48            7 FILE CAPLUS
L49            4 FILE MEDLINE
L50            1 FILE SCISEARCH
L51            0 FILE EMBASE
     TOTAL FOR ALL FILES
L52           12 S L47 AND PHOSPHODIESTERASE?
L53            2 FILE CAPLUS
L54            4 FILE MEDLINE
L55            1 FILE SCISEARCH
L56            0 FILE EMBASE
     TOTAL FOR ALL FILES
L57            7 S L52 NOT L42
L58            6 DUP REM L57 (1 DUPLICATE REMOVED)
                 E CHRONIC ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJER?
                 E CHRONIC ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJUR?
L59            0 FILE CAPLUS
L60            0 FILE MEDLINE
L61            0 FILE SCISEARCH
L62            0 FILE EMBASE
     TOTAL FOR ALL FILES
L63            0 S CHRONIC ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJUR?
L64            0 FILE CAPLUS
L65            0 FILE MEDLINE
L66            0 FILE SCISEARCH
L67            0 FILE EMBASE
     TOTAL FOR ALL FILES
L68            0 S  ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJUR?
L69            0 FILE CAPLUS
L70            0 FILE MEDLINE
L71            0 FILE SCISEARCH
L72            0 FILE EMBASE
     TOTAL FOR ALL FILES
L73            0 S  ARTERIAL ULCER? AND  PERFUSION INJUR?
L74         4195 FILE CAPLUS
L75         9087 FILE MEDLINE
L76         6734 FILE SCISEARCH
L77        15975 FILE EMBASE
     TOTAL FOR ALL FILES
L78        35991 S DIPYRIDAMOLE OR ZAPRONIST OR SILDENAFIL
L79            6 FILE CAPLUS
L80           10 FILE MEDLINE
L81            7 FILE SCISEARCH
L82           31 FILE EMBASE
     TOTAL FOR ALL FILES
L83           54 S L78 (1S) (TREAT? (1S) (WOUND? OR ULCER? OR SORE? OR DECUBITUS
L84           38 DUP REM L83 (16 DUPLICATES REMOVED)
L85           39 FILE CAPLUS
L86           17 FILE MEDLINE
L87           16 FILE SCISEARCH
L88           24 FILE EMBASE
     TOTAL FOR ALL FILES
L89           96 S DIPYRIDAMOLE AND (PHOSPHODIESTERASE (3W) (5 OR V))

     FILE 'REGISTRY' ENTERED AT 20:26:35 ON 11 JUN 2003
L90            1 S DIPYRIDAMOLE/CN

     FILE 'CAPLUS' ENTERED AT 20:27:30 ON 11 JUN 2003
L91            1 S WO2002015893/PN
L92         2415 S L90/BIOL
L93          210 S L92 AND (PHOSPHODIESTERASE)
L94           13 S L92 AND (PHOSPHODIESTERASE (2W) 5)
L95            0 S L94 AND (ULCER? OR WOUND?)
```

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L96          22 S L92 AND (ULCER? OR WOUND?)
L97           3 S L96 AND (PHOSPHODIESTERASE)
L98          13 S L90 AND (PHOSPHODIESTERASE (2W) 5)
L99           5 S DIPYRIDAMOLE (1S) (PHOSPHODIESTERASE (2W) 5)
L100          0 S DIPYRIDAMOLE (1S) LEG ULCER?
L101          0 S DIPYRIDAMOLE (2S) (LEG ULCER?)

     FILE 'CAPLUS, MEDLINE, SCISEARCH, EMBASE' ENTERED AT 20:38:22 ON 11 JUN
     2003
L102          0 FILE CAPLUS
L103          1 FILE MEDLINE
L104          0 FILE SCISEARCH
L105          4 FILE EMBASE
     TOTAL FOR ALL FILES
L106          5 S DIPYRIDAMOLE (2S) (LEG ULCER?)

     FILE 'REGISTRY' ENTERED AT 20:45:03 ON 11 JUN 2003
L107          0 S ZAPRONIST/CN
L108          0 S ZAPRONIST
L109          1 S ZAPRINAST/CN
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                SAVE L106 A09927344/L

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     FILE 'REGISTRY' ENTERED AT 20:51:57 ON 11 JUN 2003

     FILE 'CAPLUS, MEDLINE, SCISEARCH, EMBASE' ENTERED AT 20:52:06 ON 11 JUN
     2003
L110        678 FILE CAPLUS
L111        629 FILE MEDLINE
L112        545 FILE SCISEARCH
L113        936 FILE EMBASE
     TOTAL FOR ALL FILES
L114       2788 S L109 OR ZAPRINAST
L115          0 FILE CAPLUS
L116          0 FILE MEDLINE
L117          0 FILE SCISEARCH
L118          0 FILE EMBASE
     TOTAL FOR ALL FILES
L119          0 S L114 (2S) (ULCER?)
L120          0 FILE CAPLUS
L121          0 FILE MEDLINE
L122          0 FILE SCISEARCH
L123          0 FILE EMBASE
     TOTAL FOR ALL FILES
L124          0 S L114 (2S) (WOUND?)

     FILE 'CAPLUS' ENTERED AT 20:53:02 ON 11 JUN 2003
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L126       3522 S L125 AND L10 OR DIPYRIDAMOLE
L127          4 S L125 AND (10 OR DIPYRIDAMOLE)
L128          0 S L125 AND (L90 OR DIPYRIDAMOLE)
L129         21 S MMP AND (PDE5 OR PDE-5 OR (PHOSPHODIESTERASE))
L130         25 S UROKINASE AND (PDE5 OR PDE-5 OR (PHOSPHODIESTERASE))
L131          0 S L129 AND L130
L132          0 S MMP AND (PDE5 OR PDE-5)

     FILE 'CAPLUS, USPATFULL' ENTERED AT 21:28:39 ON 11 JUN 2003
L133         21 FILE CAPLUS
L134        125 FILE USPATFULL
     TOTAL FOR ALL FILES
L135        146 S MMP AND (PDE5 OR PDE-5 OR (PHOSPHODIESTERASE))
L136          0 FILE CAPLUS
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L137            7 FILE USPATFULL
     TOTAL FOR ALL FILES
L138            7 S MMP AND (PDE5 OR PDE-5 OR (PHOSPHODIESTERASE (2W) 5))
L139            0 FILE CAPLUS
L140           52 FILE USPATFULL
     TOTAL FOR ALL FILES
L141           52 S MMP AND (DIPYRIDAMOLE)
L142            0 FILE CAPLUS
L143            1 FILE USPATFULL
     TOTAL FOR ALL FILES
L144            1 S MMP (2S) (DIPYRIDAMOLE)
L145            0 FILE CAPLUS
L146            0 FILE USPATFULL
     TOTAL FOR ALL FILES
L147            0 S URIKINASE AND (PDE5 OR PDE-5 OR (PHOSPHODIESTERASE (2W) 5))
L148            0 FILE CAPLUS
L149            0 FILE USPATFULL
     TOTAL FOR ALL FILES
L150            0 S UROINASE AND (PDE5 OR PDE-5 OR (PHOSPHODIESTERASE (2W) 5))
L151            1 FILE CAPLUS
L152            5 FILE USPATFULL
     TOTAL FOR ALL FILES
L153            6 S UROKINASE AND (PDE5 OR PDE-5 OR (PHOSPHODIESTERASE (2W) 5))
L154            1 FILE CAPLUS
L155            2 FILE USPATFULL
     TOTAL FOR ALL FILES
L156            3 S L153 AND (WOUND? OR ULCER?)
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L42 ANSWER 14 OF 16 USPATFULL

ACCESSION NUMBER:	2000:150166 USPATFULL
TITLE:	Tetracyclic cyclic GMP-specific phosphodiesterase inhibitors, process of preparation and use
INVENTOR(S):	Daugan, Alain Claude-Marie, Marly le Roi Cedex, France Gellibert, Francoise, Marly le Roi Cedex, France
PATENT ASSIGNEE(S):	ICOS Corporation, Bothell, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6143746		20001107
APPLICATION INFO.:	US 1998-154051		19980916 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 1995-EP183, filed on 19 Jan 1995, now patented, Pat. No. WO 5859006 which is a continuation-in-part of Ser. No. WO 1996-EP3025, filed on 11 Jul 1996, now patented, Pat. No. WO 5981527 which is a continuation-in-part of Ser. No. WO 1996-EP3024, filed on 11 Jul 1996

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1994-1090	19940121
	GB 1995-14465	19950714
	GB 1995-14474	19950714

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Cintins, Marianne M.
ASSISTANT EXAMINER:	Delacroix-Muirheid, C.
LEGAL REPRESENTATIVE:	Marshall, O'Toole, Gerstein, Murray & Borun
NUMBER OF CLAIMS:	13
EXEMPLARY CLAIM:	1
LINE COUNT:	3174

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM In summary, the biochemical, physiological, and clinical effects of **PDE5** inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, **inflammatory**, and/or endocrine function is desirable. The compounds of formula (I), therefore, have utility in the treatment of a number of disorders, including stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, acute respiratory distress syndrome, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., postpercutaneous transluminal coronary or carotid angioplasty, or post-bypass surgery graft stenosis), peripheral vascular disease, vascular disorders, such as Raynaud's disease, thrombocythemia, **inflammatory** diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm labor, benign prostatic hypertrophy, male and female erectile dysfunction, and diseases characterized by disorders of gut motility (e.g., irritable bowel syndrome).

SUMM The present selective **PDE5** inhibitors in combination with **vasodilators**, including nitric oxide and nitric oxide donators and precursors, such as the organic nitrate **vasodilators** which act by releasing nitric oxide in vivo, are especially useful in treatment of angina, congestive heart failure, and malignant hypertension (e.g., pheochromocytoma). Related to the capacity of the present **PDE5** inhibitors to potentiate nitric oxide donors and precursors is their ability, in spontaneously hypertensive rats, to reverse the desensitization to these agents that occurs with chronic use.

SUMM Alph.alpha.-adrenergic blockers inhibit vasoconstriction in the corpus cavernosum. Because **PDE5** inhibitors enhance **vasodilation** of the same smooth muscle tissue, a **PDE5** inhibitor of formula (I) and an .alpha.-adrenergic blocker, like phentolamine or prazocin, or a centrally acting dopaminergic agent, like apomorphine, can be expected to potentiate one another in a treatment for MED or other disorders. Potentiation of mixed .alpha.,.beta.-blockers, like carvedilol, which is employed in treatment of hypertension, also is expected Similarly, .alpha..sub.2 -adrenergic blockers, like yohimbine, can be potentiated.

SUMM Angiotensin converting enzyme (ACE) inhibitors block the conversion of angiotensin I into angiotensin II, which causes systemic vasoconstriction and the retention of sodium and water. **PDE5** inhibitors cause **vasodilation** in hypertensive animals, and stimulate the excretion of sodium and water in normotensive animals. Therefore, a **PDE5** inhibitor of formula (I) can be combined with an ACE inhibitor to achieve more powerful **vasodilatory** and natriuretic effects in, for example, treatment of congestive heart failure or hypertensive states.

CLM What is claimed is:
12. A method of treating stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, malignant hypertension, pheochromocytoma, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic **ulcer**, a gut motility disorder, postpercutaneous transluminal coronary or carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy, or irritable bowel syndrome, in a human or nonhuman animal body, said method comprising administering to said body a therapeutically effective amount of a combination of claim 1.

ACCESSION NUMBER: 2001:125990 USPATFULL
TITLE: Blood pressure stabilization during hemodialysis
INVENTOR(S): Grossman, Eric B., Hasting-on-Hudson, NY, United States
PATENT ASSIGNEE(S): Pfizer Inc., New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6271228	B1	20010807
APPLICATION INFO.:	US 2001-800836		20010307 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-200439P	20000428 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Henley, III, Raymond
LEGAL REPRESENTATIVE: Richardson, Peter C., Benson, Gregg C., Musser, Arlene K.
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 650
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Lassitude, fatigue, and decreased mental acuity often are the first manifestations of uremia. In addition, other symptoms of CRF include neuromuscular features, anorexia, nausea, vomiting, stomatitis, an unpleasant taste in the mouth, malnutrition, GI **ulceration**, bleeding, cardiomyopathy (hypertensive, ischemic), and ultimately congestive heart failure or dependent edema.

DETD Cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE) inhibitors are widely known as cardiovascular agents for the treatment of conditions such as angina, hypertension, and congestive heart failure. U.S. Pat. No. 5,250,534, incorporated herein by reference, discloses a class of cyclic guanosine 3'5'-monophosphate (cGMP) **phosphodiesterase** type **5** (**PDE5**) inhibitors useful in the treatment of, for example, angina. One member of this class is sildenafil, which has two chemical names: 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1 H-pyrazolo[4,3-d]pyrimidin-5-yl)4-ethoxyphenyl]sulfonyl]-4-methylpiperazine and 5-[2-ethoxy-5-(4-methylpiperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one. Sildenafil citrate is sold under the tradename Viagra.RTM. by Pfizer Inc. and indicated for the treatment of erectile dysfunction. Physician's Desk Reference 2424-2426 (53.sup.rd ed. 1999). By slowing the rate of cGMP breakdown, sildenafil enhances the **vasodilatory** effect of naturally produced NO.

```
      (FILE 'HOME' ENTERED AT 17:30:52 ON 11 JUN 2003)

      FILE 'CAPLUS, USPATFULL, PCTFULL' ENTERED AT 17:36:10 ON 11 JUN 2003
L1           401 FILE CAPLUS
L2           113 FILE USPATFULL
L3             0 FILE PCTFULL
      TOTAL FOR ALL FILES
L4           514 S 139755-83-2/RN
L5           407 FILE CAPLUS
L6             0 FILE USPATFULL
L7             0 FILE PCTFULL
      TOTAL FOR ALL FILES
L8           407 S 139755-83-2
L9           710 FILE CAPLUS
L10          397 FILE USPATFULL
L11          440 FILE PCTFULL
      TOTAL FOR ALL FILES
L12         1547 S SILDENAFIL
L13          728 FILE CAPLUS
L14          412 FILE USPATFULL
L15          440 FILE PCTFULL
      TOTAL FOR ALL FILES
L16         1580 S L4 OR L8 OR L12
L17          118 FILE CAPLUS
L18           79 FILE USPATFULL
L19          160 FILE PCTFULL
      TOTAL FOR ALL FILES
L20          357 S L16 (2S) (WOUND? OR ULCER? OR SORE? OR CUT? OR GRAZE? OR HEMO
L21           10 FILE CAPLUS
L22           30 FILE USPATFULL
L23           54 FILE PCTFULL
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L24           94 S L16 (2S) (WOUND? OR ULCER? OR SORE? OR CUT? OR GRAZE? OR HEMO
L25            0 FILE CAPLUS
L26           16 FILE USPATFULL
L27           46 FILE PCTFULL
      TOTAL FOR ALL FILES
L28           62 S (L16 (2S) (VASODILAT? OR INFLAMMAT?)) AND (TREAT? (1S)( WOUND
L29         1171 FILE CAPLUS
L30          450 FILE USPATFULL
L31          401 FILE PCTFULL
      TOTAL FOR ALL FILES
L32         2022 S (PDE 5) OR (PDE-5) OR (PDE5) OR (PHOSPHODIESTERASE (3W) 5)
L33            6 FILE CAPLUS
L34           16 FILE USPATFULL
L35           83 FILE PCTFULL
      TOTAL FOR ALL FILES
L36          105 S (L32 (2S) (VASODILAT? OR INFLAMMAT?)) AND (TREAT? (1S)( WOUND
L37            6 FILE CAPLUS
L38           12 FILE USPATFULL
L39           72 FILE PCTFULL
      TOTAL FOR ALL FILES
L40           90 S L36 NOT L28
L41            7 FILE CAPLUS
L42           16 FILE USPATFULL
L43           80 FILE PCTFULL
      TOTAL FOR ALL FILES
L44          103 S (L32 (2S) (VASODILAT? OR INFLAMMAT?)) AND ( WOUND? OR ULCER?
L45        24124 FILE CAPLUS
L46         7295 FILE USPATFULL
L47         5499 FILE PCTFULL
      TOTAL FOR ALL FILES
L48        36918 S (PDE) OR (PDE?) OR (PHOSPHODIESTERASE)
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L49         3888 FILE CAPLUS
L50         1329 FILE USPATFULL
L51         1168 FILE PCTFULL
     TOTAL FOR ALL FILES
L52         6385 S ((PDE) OR (PDE?)) AND (?PHOSPHODIESTERASE?)
L53           32 FILE CAPLUS
L54          411 FILE USPATFULL
L55          478 FILE PCTFULL
     TOTAL FOR ALL FILES
L56          921 S L52 (2S) (TREAT? (1S)( WOUND? OR ULCER? OR SORE?))
L57            6 FILE CAPLUS
L58          155 FILE USPATFULL
L59          201 FILE PCTFULL
     TOTAL FOR ALL FILES
L60          362 S L56 AND (CGMP)

     FILE 'CAPLUS' ENTERED AT 18:25:37 ON 11 JUN 2003
                SELECT L57 6 RN
L61            3 S E1-E91
L62            0 S L61 AND ((PDE 5) OR (PDE-5) OR (PDE5) OR (PHOSPHODIESTERASE (

=> s l56 not ulcerative
L63           11 L53 NOT ULCERATIVE
```

553051 19990611

L27 ANSWER 59 OF 1154 CAPLUS COPYRIGHT 2003 ACS
TI **Nitric oxide** inhibits wound collagen synthesis
AB **Nitric oxide** (NO) is a messenger mol. which regulates many physiol. functions like immunity, vascular tone and serves as a neurotransmitter. Although it is known to participate in healing process, its role in collagen synthesis is not clear. Therefore, the present investigation was done to study the role of NO in **wound** collagen synthesis. Rats received full thickness, circular (8 mm), transdermal **wounds** which were **treated** with NO releaser, sodium nitroprusside (SNP, 0.001 100 .mu.M) topically for 5 days. **Wound** collagen content estd. in terms of hydroxyproline (HP) and confirmed histochem. was decreased significantly by all SNP doses. L-Arginine, a substrate for **nitric oxide** synthase (NOS) when applied topically decreased collagen content of the **wounded** tissues. N-Nitro-L-arginine Me ester (L-NAME), a competitive inhibitor of NOS, increased **wound** collagen content significantly as compared to untreated and SNP **treated** animal **wounds** when administered i.p. at the doses 3, 10 and 30 mg/kg. Furthermore, histol. findings also demonstrated laying down of thick collagen bundles and proliferation of fibroblasts together with prominent angiogenesis in L-NAME **treated wound** tissues as compared to untreated and SNP **treated** tissues. N-nitro-D-arginine Me ester, an inactive isomer, was found to have no effect on **wound** collagen levels. When L-arginine was administered in L-NAME pretreated rats, it significantly elevated wound HP content. The results indicate that NO plays an important role in regulating the collagen biosynthesis in skin model of a healing wound.
ST **nitric oxide** collagen formation wound healing
IT Wound healing
(**nitric oxide** regulation of wound collagen synthesis)
IT Collagens, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PROC (Process)
(**nitric oxide** regulation of wound collagen synthesis)
IT 10102-43-9, **Nitric oxide**, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**nitric oxide** regulation of wound collagen synthesis)

L27 ANSWER 60 OF 1154 CAPLUS COPYRIGHT 2003 ACS
TI **Nitric oxide** triggers enhanced induction of vascular endothelial growth factor expression in cultured keratinocytes (HaCaT) and during cutaneous wound repair
AB Recently, we demonstrated a large induction of inducible **nitric oxide** synthase (iNOS) during cutaneous wound repair. In this study, we investigated the role of **nitric oxide** (NO) for the expression of vascular endothelial growth factor (VEGF), which represents the most important angiogenic factor during the proliferative phase of skin repair. Since keratinocytes are the major source of VEGF prodn. during this process, we used cultured keratinocytes (HaCaT cell line) as an in vitro model to investigate NO action on growth factor and cytokine-stimulated VEGF expression. Exogenously added NO enhanced transforming growth factor-.beta.1-, keratinocyte growth factor-, interleukin-1.beta.-, tumor necrosis factor-.alpha.-, and interferon-.gamma.-induced VEGF mRNA and protein synthesis in keratinocytes. We could demonstrate that high-level expression of cytokine-induced VEGF mRNA in keratinocytes is dependent on endogenously

produced NO, as inhibition of the coinduced iNOS by NG-monomethyl-L-arginine (L-NMMA) markedly decreased cytokine-triggered VEGF mRNA levels in the cells. We also established an in vivo model in mice to investigate the role of NO during **wound** healing. During excisional **wound** repair, mice were **treated** with L-N6-(1-iminoethyl)lysine (L-NIL), a selective inhibitor of iNOS enzymic activity. Compared to control mice, L-NIL-**treated** animals were characterized by markedly reduced VEGF mRNA levels during the inflammatory phase of repair. Immunohistochem. demonstrated reduced VEGF protein expression and a completely disorganized pattern of VEGF-expressing keratinocytes within the hyperproliferative epithelium at the **wound** edge in L-NIL-**treated** mice. We demonstrate that triggering of VEGF expression is a crucial mol. mechanism underlying NO function during **wound** healing.

ST **nitric oxide** VEGF keratinocyte wound repair

IT Skin
(keratinocyte; **nitric oxide** triggers enhanced induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

IT Transcription, genetic
(**nitric oxide** triggers enhanced cytokine induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

IT Interleukin 1.beta.
Tumor necrosis factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**nitric oxide** triggers enhanced cytokine induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

IT Wound healing
(**nitric oxide** triggers enhanced induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

IT Skin, disease
(wound; **nitric oxide** triggers enhanced induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

IT Transforming growth factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.1-; **nitric oxide** triggers enhanced cytokine induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(.gamma.; **nitric oxide** triggers enhanced cytokine induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

IT 148348-15-6, Fibroblast growth factor 7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**nitric oxide** triggers enhanced cytokine induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

IT 10102-43-9, **Nitric oxide**, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**nitric oxide** triggers enhanced induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

IT 125978-95-2, **Nitric oxide** synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**nitric oxide** triggers enhanced induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

IT 127464-60-2, Vascular endothelial growth factor
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**nitric oxide** triggers enhanced induction of VEGF expression in cultured keratinocytes and during cutaneous wound repair)

L27 ANSWER 79 OF 1154 CAPLUS COPYRIGHT 2003 ACS

TI **Nitric oxide** regulates wound healing

AB **Nitric oxide** (NO) synthesis occurs during wound healing, but its role has not been defined. To study the effect of NO on wound repair, S-Me isothiouronium (MITU, a competitive inhibitor of NO synthase) was administered at a dose of 10, 50, and 100 mg/kg body wt./day, using i.p. implanted miniosmotic pumps. Groups of 10 male Balb/C mice underwent a dorsal skin incision and polyvinyl alc. sponges were inserted s.c. The animals were sacrificed 10 days postwounding and wound breaking strength and hydroxyproline content of sponges, an index of reparative collagen deposition, were detd. Some sponges were used to harvest wound fluid and infiltrating cells, which were then incubated overnight with or without 1 mM MITU. Nitrite and nitrate, stable end products of NO, were measured in wound fluid and in wound cell culture supernatants. Continuous i.p. infusion of MITU decreased wound fluid nitrite/nitrate concns. in a dose-dependent manner. Inhibition of **wound** NO synthesis by 100 mg MITU/kg/day was paralleled by lowered **wound** collagen accumulation and **wound**-breaking strength. In vitro NO synthesis by **wound** cells obtained from animals **treated** with 100 mg MITU/kg/day was not different from controls (12.6 vs. 10.7 nmole NO2 + NO3/.mu.g DNA), reflecting the reversible inhibition of NO synthase by MITU. However, NO prodn. was equally inhibited in **wound** infiltrating cells by the in vitro addn. of MITU (83% vs. 85%, resp.). Apparently, **nitric oxide** synthesis is crit. to wound collagen accumulation and acquisition of mech. strength.

ST **nitric oxide** skin wound collagen strength

IT Wound healing
(**nitric oxide** synthesis is crit. to wound collagen accumulation and acquisition of mech. strength)

IT Collagens, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**nitric oxide** synthesis is crit. to wound collagen accumulation and acquisition of mech. strength)

IT Skin, disease
(wound, **nitric oxide** synthesis is crit. to wound collagen accumulation and acquisition of mech. strength)

IT 10102-43-9, **Nitric oxide**, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**nitric oxide** synthesis is crit. to wound collagen accumulation and acquisition of mech. strength)

ACCESSION NUMBER: 1996:447509 CAPLUS
DOCUMENT NUMBER: 125:111829
TITLE: **Nitric oxide** regulates wound healing
AUTHOR(S): Schaffer, Michael R.; Tantry, Udaya; Gross, Steven S.; Wasserkrug, Hannah L.; Barbul, Adrian
CORPORATE SOURCE: Department Surgery, Sinai Hospital Baltimore, Baltimore, MD, 21218, USA
SOURCE: Journal of Surgical Research (1996), 63(1), 237-240
CODEN: JSGRA2; ISSN: 0022-4804
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

L27 ANSWER 78 OF 1154 CAPLUS COPYRIGHT 2003 ACS
TI **Nitric oxide** is decreased in diabetic wound healing
AB Wound collagen deposition and mech. strength were decreased in diabetic wound healing in rats. Impaired healing was reflected in decreased **wound** NO and lowered cellular capability to produce NO. **Wound** healing and NO synthesis were partially restored by insulin **treatment**.
ST **nitric oxide** wound healing diabetes insulin
IT 10102-43-9P, **Nitric oxide**, biological studies
RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(NO decreased in diabetic wound healing)

ACCESSION NUMBER: 1997:402648 CAPLUS
DOCUMENT NUMBER: 127:134188
TITLE: **Nitric oxide** is decreased in diabetic wound healing
AUTHOR(S): Schaffer, Michael; Tantry, U.; Efron, P.; Ahrendt, G.; Becker, H. D.; Barbul, A.
CORPORATE SOURCE: Chirurgische Klinik, Universitat Tubingen, Tuebingen, D-72076, Germany
SOURCE: Chirurgisches Forum fuer Experimentelle und Klinische Forschung (1997) 519-521
CODEN: CFEKA7; ISSN: 0303-6227
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: German

L84 ANSWER 32 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AB An animal model suitable for study of the origin and method of prevention of thromboembolic complications of arterial prostheses has been developed in the rabbit. In phase I of the experiments 42 New Zealand white rabbits underwent insertion of polytetrafluoroethylene (PTFE) aortic grafts, 10 mm in length and of 2 mm internal diameter (I.D.) (n=17) and 3 mm I.D.(n=25). The patency rate at 3 months was 24% and 82%, respectively. Unexpected ischemic hind limb **ulcers** occurred in nine (38%) of the long-term survivors. Arteriograms in these animals showed a typical embolic occlusion of a distal artery, suggesting that the **ulcers** were due to embolization of loose mural thrombus, which was present in 50% of the grafts when removed. In phase II experiments 54 rabbits were randomly allocated to receive aspirin (ASA) 10 mg/kg/day and **dipyridamole** (DPM) 10 mg/kg/day (n=25)or placebo (n=29). Both regimens began 3 days before insertion of PTFE aortic grafts (10 mm long and 3 mm I.D.). Serum thromboxane B2 concentrations in the control group averaged 300.4 .+-. 147.4 ng/ml and 43.2 .+-. 58.6 ng/ml in the ASA/DPM group ($p<0.0005$). With the use of autologous indium 111 oxine-labeled platelets, a graft platelet accumulation index (GPAI) was calculated as the graft:reference ratio of emissions. ASA/DPM significantly reduced the mean GPAI calculated from grafts and reference aorta removed 48 hours after graft insertion from 69.3 .+-. 4.0 on placebo (n=4) to 34.3 .+-. 2.9 (n=4) ($p<0.001$). At 3 months eight (33%) of the remaining 24 control animals had hind limb **ulcers** 31.0 .+-. 22.5 days post-operatively, whereas none occurred among the 19 animals **treated** with antiplatelet agents ($p<0.01$). This correlation of ASA/DPM reduction of platelet accumulation on PTFE grafts with prevention of thromboembolic complications suggests that patients receiving small-diameter PTFE grafts should be considered candidates for long-term antiplatelet therapy.

L84 ANSWER 33 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AB The **dipyridamole** and aspirin therapy outlined in the table is standard at the Mayo Clinic and Mount Sinai Hospitals for patients undergoing aortocoronary vein bypass operations. For patients who are allergic to or intolerant of aspirin or who have had previous gastrointestinal bleeding or gastric **ulcer**, there are two empiric alternatives: continue **dipyridamole**, 100 mg four times daily, without aspirin after operation, or use sulfinpyrazone, 200 mg four times daily, beginning 1 or 2 days before operation and continuing on the day of and after operation (one trial showing favorable benefit has been discussed). Platelt inhibitor therapy should be continued for at least one year and perhaps indefinitely, as suggested by the decreased lipid incorporation into vein grafts after administration of **dipyridamole** and aspirin in nonhuman primates. The ultimate results of our ongoing trial in the prevention of angiographic progression of coronary artery disease over 5 years in patients **treated** with **dipyridamole** and aspirin but without aortocoronary bypass surgery should also be helpful in determining whether therapy should be continued indefinitely.

ACCESSION NUMBER: 85059272 EMBASE
DOCUMENT NUMBER: 1985059272
TITLE: Perioperative antiplatelet therapy for aortocoronary artery bypass surgery.
AUTHOR: Chesebro J.H.; Fuster V.
CORPORATE SOURCE: Mayo Clinic and Mayo Foundation, Rochester, MN 55905, United States
SOURCE: Modern Concepts of Cardiovascular Disease, (1984) 53/12 (65-70).
CODEN: MCCDAV
COUNTRY: United States

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     (FILE 'HOME' ENTERED AT 19:30:11 ON 11 JUN 2003)

     FILE 'CAPLUS, USPATFULL' ENTERED AT 19:30:36 ON 11 JUN 2003
L1         3165 FILE CAPLUS
L2         1392 FILE USPATFULL
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L3         4557 S (PDE OR PDR?) AND PHOSPHODIESTERASE
L4           12 FILE CAPLUS
L5          487 FILE USPATFULL
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L6          499 S L3 AND (TREAT? (1S) (WOUND? OR ULCER? OR SORE? IR DECUBITUS))
L7           12 FILE CAPLUS
L8          489 FILE USPATFULL
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L9          501 S L3 AND (TREAT? (1S) (WOUND? OR ULCER? OR SORE? OR DECUBITUS))
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L11          43 FILE USPATFULL
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L12           43 S L9 AND L3/CLM
L13        91518 FILE CAPLUS
L14         9896 FILE USPATFULL
     TOTAL FOR ALL FILES
L15       101414 S (NITRIC OXIDE OR CGMP )
L16        91518 FILE CAPLUS
L17         9896 FILE USPATFULL
     TOTAL FOR ALL FILES
L18       101414 S L15
L19          224 FILE CAPLUS
L20         1843 FILE USPATFULL
     TOTAL FOR ALL FILES
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L22          113 FILE CAPLUS
L23          167 FILE USPATFULL
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L25           82 FILE CAPLUS
L26         1072 FILE USPATFULL
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L27         1154 S L18 AND (TREAT? (1S) (WOUND? OR (VENOUS ULCER?) OR (ATERIAL U

     FILE 'CAPLUS, MEDLINE, SCISEARCH, EMBASE' ENTERED AT 19:52:21 ON 11 JUN
     2003
L28           82 FILE CAPLUS
L29           52 FILE MEDLINE
L30           88 FILE SCISEARCH
L31           73 FILE EMBASE
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L32          295 S L27
L33            0 FILE CAPLUS
L34            0 FILE MEDLINE
L35            0 FILE SCISEARCH
L36            0 FILE EMBASE
     TOTAL FOR ALL FILES
L37            0 S L32 AND L3
L38            5 FILE CAPLUS
L39            0 FILE MEDLINE
L40            0 FILE SCISEARCH
L41            0 FILE EMBASE
     TOTAL FOR ALL FILES
L42            5 S L32 AND PHOSPHODIESTERASE?
L43          465 FILE CAPLUS
L44          485 FILE MEDLINE
L45          426 FILE SCISEARCH
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L46          364 FILE EMBASE
     TOTAL FOR ALL FILES
L47         1740 S L18 AND ( (WOUND? OR (VENOUS ULCER?) OR (ATERIAL ULCER?) OR S
L48            7 FILE CAPLUS
L49            4 FILE MEDLINE
L50            1 FILE SCISEARCH
L51            0 FILE EMBASE
     TOTAL FOR ALL FILES
L52           12 S L47 AND PHOSPHODIESTERASE?
L53            2 FILE CAPLUS
L54            4 FILE MEDLINE
L55            1 FILE SCISEARCH
L56            0 FILE EMBASE
     TOTAL FOR ALL FILES
L57            7 S L52 NOT L42
L58            6 DUP REM L57 (1 DUPLICATE REMOVED)
                 E CHRONIC ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJER?
                 E CHRONIC ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJUR?
L59            0 FILE CAPLUS
L60            0 FILE MEDLINE
L61            0 FILE SCISEARCH
L62            0 FILE EMBASE
     TOTAL FOR ALL FILES
L63            0 S CHRONIC ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJUR?
L64            0 FILE CAPLUS
L65            0 FILE MEDLINE
L66            0 FILE SCISEARCH
L67            0 FILE EMBASE
     TOTAL FOR ALL FILES
L68            0 S  ARTERIAL ULCER? AND ISCHEMIC PERFUSION INJUR?
L69            0 FILE CAPLUS
L70            0 FILE MEDLINE
L71            0 FILE SCISEARCH
L72            0 FILE EMBASE
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L73            0 S  ARTERIAL ULCER? AND  PERFUSION INJUR?
L74         4195 FILE CAPLUS
L75         9087 FILE MEDLINE
L76         6734 FILE SCISEARCH
L77        15975 FILE EMBASE
     TOTAL FOR ALL FILES
L78        35991 S DIPYRIDAMOLE OR ZAPRONIST OR SILDENAFIL
L79            6 FILE CAPLUS
L80           10 FILE MEDLINE
L81            7 FILE SCISEARCH
L82           31 FILE EMBASE
     TOTAL FOR ALL FILES
L83           54 S L78 (1S) (TREAT? (1S) (WOUND? OR ULCER? OR SORE? OR DECUBITUS
L84           38 DUP REM L83 (16 DUPLICATES REMOVED)
L85           39 FILE CAPLUS
L86           17 FILE MEDLINE
L87           16 FILE SCISEARCH
L88           24 FILE EMBASE
     TOTAL FOR ALL FILES
L89           96 S DIPYRIDAMOLE AND (PHOSPHODIESTERASE (3W) (5 OR V))

     FILE 'REGISTRY' ENTERED AT 20:26:35 ON 11 JUN 2003
L90            1 S DIPYRIDAMOLE/CN

     FILE 'CAPLUS' ENTERED AT 20:27:30 ON 11 JUN 2003
L91            1 S WO2002015893/PN
L92         2415 S L90/BIOL
L93          210 S L92 AND (PHOSPHODIESTERASE)
L94           13 S L92 AND (PHOSPHODIESTERASE (2W) 5)
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L95             0 S L94 AND (ULCER? OR WOUND?)
L96            22 S L92 AND (ULCER? OR WOUND?)
L97             3 S L96 AND (PHOSPHODIESTERASE)

=>
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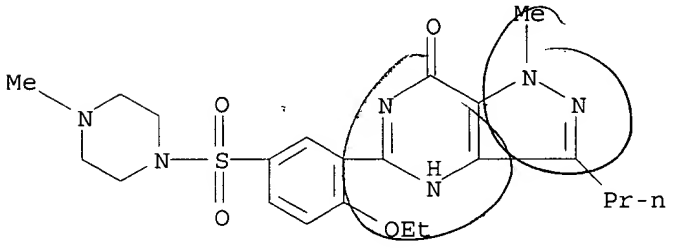
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 139755-83-2 REGISTRY
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrazolo[4,3-d]pyrimidine, piperazine deriv.
OTHER NAMES:
CN 5-[2-Ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one
CN **Sildenafil**
FS 3D CONCORD
MF C22 H30 N6 O4 S
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO

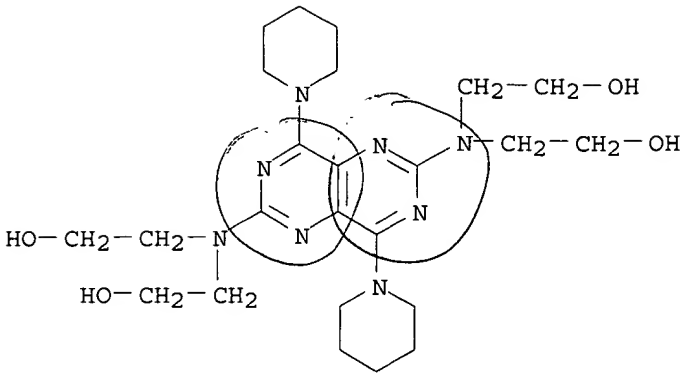


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

405 REFERENCES IN FILE CA (1957 TO DATE)
7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
407 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=>

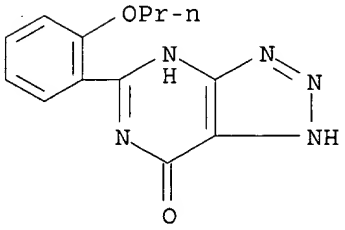
L90 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 58-32-2 REGISTRY
CN Ethanol, 2,2',2'',2'''-[(4,8-di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ethanol, 2,2',2'',2'''-[(4,8-dipiperidinopyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetra- (6CI, 8CI)
CN Pyrimido[5,4-d]pyrimidine, ethanol deriv.
OTHER NAMES:
CN 2,2',2'',2'''-[[4,8-Dipiperidinopyrimido(5,4-d)pyrimidine-2,6-diyl]dinitrilo]tetraethanol
CN 2,6-Bis(diethanolamino)-4,8-dipiperidinopyrimido[5,4-d]pyrimidine
CN Anginal
CN Apricor
CN Cardioflux
CN Cardoxil
CN Cardoxin
CN Cleridium
CN Coribon
CN Coridil
CN Coronarine
CN Corosan
CN Coroxin
CN Curantyl
CN Dipyridamine
CN Dipyridamol
CN **Dipyridamole**
CN Dipyridan
CN Gulliostin
CN Kurantil
CN Natyl
CN NSC 515776
CN Peridamol
CN Persantin
CN Persantine
CN Piroan
CN Prandiol
CN Protangix
CN RA 8
CN Stenocardil
CN Stimolcardio
FS 3D CONCORD
MF C24 H40 N8 O4
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGPAT, DRUGU, EMBASE, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2854 REFERENCES IN FILE CA (1957 TO DATE)
32 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2857 REFERENCES IN FILE CAPLUS (1957 TO DATE)
74 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L109 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 37762-06-4 REGISTRY
CN 7H-1,2,3-Triazolo[4,5-d]pyrimidin-7-one, 1,4-dihydro-5-(2-propoxyphenyl)-
(9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-(2-Propoxyphenyl)-8-aza-6-purinone
CN 2-(o-Propoxyphenyl)-8-azapurin-6-one
CN 8-Aza-2-(2-propoxyphenyl)-6-purinone
CN M and B 22948
CN M&B 22,948
CN **Zaprinast**
FS 3D CONCORD
DR 55122-20-8
MF C13 H13 N5 O2
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS,
BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMLIST,
CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PHAR,
PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

342 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
341 REFERENCES IN FILE CAPLUS (1957 TO DATE)

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L12 ANSWER 84 OF 90 USPATFULL

AB Disclosed is a biocompatible, thromboresistant substance useful for implantable and extracorporeal devices in contact with the vascular system, and methods for producing the same. The biocompatible, thromboresistant substance comprises a synthetic, biocompatible material, at least one biocompatible base coat layer adhered to at least one surface of the material, and a thrombogenesis inhibitor immobilized on the base coat layer via a component capable of binding the inhibitor. The thrombogenesis **inhibitor** is streptokinase, **urokinase**, tissue plasminogen activator, ATPase, 5'-nucleotidase, and active fragments and active analogs thereof.

SUMM To decrease the chances of thrombosis due to extended periods of contact with such artificial materials, patients have been treated with systemically administered anti-coagulant, anti-platelet, and thrombolytic drugs. These include any compound which selectively inhibits thromboxane synthetase without affecting prostacycline synthetase, affects platelet adherence as well as aggregation and release, enhances vascular PGI2 production, and/or inhibits both thrombin- and thromboxane-mediated platelet aggregation. Such compounds include aspirin, sulfinpyrazone, **dipyridamole**, ticlopidine, and suloctidil. However, treatment with these drugs often elicits unwanted side effects including systemic hemmorhaging and the inability to initiate and complete desired clotting elsewhere in the body.

PI US 5019393 19910528

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L16 ANSWER 14 OF 14 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 82140295 EMBASE
DN 1982140295
TI Atrophie blanche. Report of two patients treated with aspirin and dipyridamole.
AU Kern A.B.
CS Subsect., Dermatol., Sch. Med., Brown Univ., Providence, RI, United States
SO Journal of the American Academy of Dermatology, (1982) 6/6 (1048-1053). CODEN: JAADDB
CY United States
DT Journal
FS 013 Dermatology and Venereology
LA English
AB Atrophie blanche was originally attributed to syphilis or tuberculosis, but recent investigators have generally implicated a localized cutaneous **vasculitis**. In an attempt to inhibit the occlusive vascular changes believed responsible for the cutaneous lesions, drugs such as phenformin and ethylestrenol, which increased the blood fibrinolytic activity, were used with favorable results. When phenformin was taken off the market, the use of drugs that act by preventing platelet aggregation was suggested by encouraging results in the management of other occlusive vascular disorders such as coronary artery disease and stroke. Excellent results are reported in two cases of atrophie blanche treated with two anti-platelet-aggregating medications, aspirin and **dipyridamole** (Persantine). It is imperative that low doses of aspirin be used, since high doses have the effect of increasing the thrombotic tendency by preventing prostacyclin formation.
CT Medical Descriptors:
*skin depigmentation
fibrinolysis
thrombocyte aggregation
vasculitis
case report
therapy
peripheral vascular system
Drug Descriptors:
*acetylsalicylic acid
*dipyridamole
RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2

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L16 ANSWER 13 OF 14 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 82199404 EMBASE
DN 1982199404
TI Antiplatelet therapy in atrophie blanche and livedo vasculitis.
AU Drucker C.R.; Duncan W.C.
CS Dept. Dermatol., Baylor Coll. Med., Houston, TX, United States
SO Journal of the American Academy of Dermatology, (1982) 7/3 (359-363).
CODEN: JAADDB
CY United States
DT Journal
FS 013 Dermatology and Venereology
025 Hematology
037 Drug Literature Index
LA English
AB Seven patients with atrophie blanche or livedo **vasculitis** of the lower extremities showed abnormal platelet functions in vitro. Six of seven showed hyperaggregation with epinephrine and/or collagen, three showed increased platelet adhesiveness, theee showed increased platelet count, and one showed increased microemboli. After treatment with **dipyridamole** and aspirin, all showed return to normal platelet function. Clinical improvement occurred in all patients, with signficant alleviation of pain and decrease in new lesion formation. Although enhanced healing of lesions seemed evident to physician and patient, it was incomplete. In two patients, pain returned when **dipyridamole** and aspirin were stopped, but the patients improved again when the medicines were restarted. These preliminary findings indicate a possible beneficial effect of antiplatelet therapy in atrophie blanche and livedo **vasculitis**. A double-blind study is being undertaken to further study this effect.
CT Medical Descriptors:
*atrophie blanche
*livedo
*thrombocyte
*thrombocyte aggregation inhibition
*vasculitis
therapy
thrombocyte adhesiveness
peripheral vascular system
blood and hemopoietic system
Drug Descriptors:
*acetylsalicylic acid
*dipyridamole
adenosine diphosphate
adrenalin
aldesulfone
antibiotic agent
collagen
corticosteroid
dextranomer
ethylestrenol
methyltestosterone
phenformin
serotonin
thrombin
RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (adenosine diphosphate) 20398-34-9, 58-64-0; (adrenalin) 51-43-4, 55-31-2, 6912-68-1; (aldesulfone) 144-75-2, 144-76-3; (collagen) 9007-34-5; (dextranomer) 56087-11-7; (ethylestrenol) 965-90-2; (methyltestosterone) 58-18-4; (phenformin) 114-86-3, 834-28-6; (serotonin) 50-67-9; (thrombin) 9002-04-4
CN Aspirin; Debrisan

L16 ANSWER 9 OF 14 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 94197409 EMBASE
DN 1994197409
TI Three cases of livedo **vasculitis** cleared by combined therapy of acetylsalicylic acid, **dipyridamole** and nifedipine.
AU Yoon T.Y.; Chang S.H.
CS Department of Dermatology, College of Medicine, Chungbuk National University,Cheongju, Korea, Republic of
SO Korean Journal of Dermatology, (1994) 32/2 (294-299).
ISSN: 0494-4739 CODEN: TPKCAW
CY Korea, Republic of
DT Journal; Article
FS 013 Dermatology and Venereology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA Japanese
SL English
AB Livedo **vasculitis** clinically shows purpuric papules and recurrent ulcers in the lower extremities, mainly on the ankles, leaving characteristic scars called atrophie blanche after the healing of the ulcers. Its characteristic histopathologic features and clinical evolution indicate that the common pathologic event is occlusion of vessels in the middle and deep dermis. In Korean literature, seven cases of this disease have been reported but the response of the treatment was not satisfactory. We report three cases of livedo **vasculitis** cleared by combined therapy of acetylsalicylic acid, **dipyridamole** and nifedipine, which has not been reported in Korean literature.
CT Medical Descriptors:
*skin ulcer: DT, drug therapy
*vasculitis: DT, drug therapy
article
case report
human
recurrent peptic ulcer
ulcer healing
Drug Descriptors:

L16 ANSWER 8 OF 14 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 95047816 EMBASE
DN 1995047816
TI Reduced red blood cell deformability in patients with rheumatoid **vasculitis**: Improvement after in vitro treatment with **dipyridamole**.
AU Lau C.S.; Saniabadi A.R.; Belch J.J.F.
CS Department of Medicine, University of Hong Kong, Queen Mary Hospital,Hong Kong, Hong Kong
SO Arthritis and Rheumatism, (1995) 38/2 (248-253).
ISSN: 0004-3591 CODEN: ARHEAW
CY United States
DT Journal; Article
FS 031 Arthritis and Rheumatism
037 Drug Literature Index
LA English
SL English
AB Objective. To assess red blood cell deformability (RCD) in patients with rheumatoid arthritis (RA) without extraarticular manifestations and in RA with vasculitic complications (RV), and to assess whether in vitro dipyridamole improves RCD. Methods. An improved filtration technique was used to measure RCD in 15 patients with RA, 18 patients with RV, and 20 age- and sex-matched normal control subjects. Washed erythrocytes suspended in buffer, at 5% hematocrit, were filtered through 4.7.mu. Nuclepore Hemafil PC membranes. The initial steady-state relative filtration pressure (iRFP) was used as an index to assess RCD. A lower iRFP value reflects increased deformability, a higher value reflects a decrease. For each sample, 2 cell suspensions were prepared, one blank (control) and one containing 5 .mu.M dipyridamole. Results. The mean iRFP values of cells obtained from patients with RV were significantly higher than those of cells obtained from normal controls. There were no appreciable differences in iRFP between RA patients and normal controls. When the erythrocytes were pretreated in vitro with 5 .mu.M dipyridamole before filtration, their deformability improved markedly (iRFP values were reduced) in all study subjects, compared with untreated cells. Conclusion. RCD is reduced in patients with RV, and treatment with dipyridamole may be beneficial if reduced RCD contributes to impaired microvascular perfusion.
CT Medical Descriptors:
*erythrocyte deformability
*rheumatoid arthritis: DT, drug therapy
*rheumatoid arthritis: DI, diagnosis
*vasculitis: CO, complication
*vasculitis: ET, etiology
*vasculitis: DI, diagnosis
adult
aged
article
blood filtration
clinical article
clinical feature
controlled study
disease association
erythrocyte count
female
human

L16 ANSWER 5 OF 14 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 96126259 EMBASE
DN 1996126259
TI [Livedo **vasculitis** with summer ulceration. Therapy with pentoxifylline and **dipyridamole**].
VASCULITIS LIVEDOIDE CON ULCERAS DE VERANO. TRATAMIENTO CON PENTOXIFILLINA Y DIPIRADAMOL.
AU Just M.; Ribera M.; Bielsa I.; Paradelo C.; Ferrandiz C.
CS Servicio de Dermatologia, Hosp. Univ. Germans Trias i Pujol, Ctra. del Caryet, s/n,08916 Badalona, Spain
SO Actas Dermo-Sifiliograficas, (1996) 87/4 (199-203).
ISSN: 0001-7310 CODEN: ADSIAZ
CY Spain
DT Journal; Article
FS 013 Dermatology and Venereology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA Spanish
SL Spanish; English
AB Livedo **vasculitis** with summer ulceration appears as painful ulcerations on the lower legs. Histologically, it shows thrombotic occlusion of small vessels in the middle dermis without **vasculitis**. Although this condition has been reported in association with several systemic diseases, most cases seem to be idiopathic. Three cases which dramatically improve by combination treatment with pentoxifylline and **dipyridamole** are reported. Pentoxifylline has multiple mechanisms of action, most of which may contribute to its successful use in the treatment of idiopathic livedo **vasculitis**.
CT Medical Descriptors:
*leg ulcer: DT, drug therapy
adult
article
case report
drug efficacy
female
histology
human
male
oral drug administration
segmented hyalinizing vasculitis: DT, drug therapy
thrombosis
Drug Descriptors:
*dipyridamole: DT, drug therapy
*dipyridamole: CB, drug combination
*pentoxifylline: DT, drug therapy
*pentoxifylline: CB, drug combination
RN (dipyridamole) 58-32-2; (pentoxifylline) 6493-05-6

L23 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 2001:49946 CAPLUS
DN 135:116856
TI Stasis ulcers refractory to therapy-accelerated healing by treatment with clopidogrel .+-. dalteparin: A preliminary report
AU Bick, Rodger L.; Scott, Ronald G.
CS Clinical Professor of Medicine & Pathology, University of Texas Southwestern Medical Center, Dallas, TX, 75231, USA
SO Clinical and Applied Thrombosis/Hemostasis (2001), 7(1), 21-24
CODEN: CATHF9; ISSN: 1076-0296
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 1-8 (Pharmacology)
AB Stasis **ulcers** are commonly the result of chronic **venous** insufficiency. We have recently assessed 15 patients with stasis **ulcers** that failed to heal after one year of routine wound care. All patients demonstrated a defect in hemostasis, and a biopsy revealed livido **vasculitis**. Eleven of fifteen patients were treated with clopidogrel and dalteparin, and 4 of 15 patients were treated with clopidogrel alone. Thirteen of fifteen patients (86.6%) completely healed within three months of starting antithrombotic therapy. Patients with stasis **ulcers** and chronic **venous** insufficiency who fail to heal with routine wound care should be subjected to biopsy, a procoagulant defect evaluation, and initiation of clopidogrel and dalteparin therapy if a defect is found.
ST dalteparin clopidogrel stasis ulcer
IT Skin preparations (pharmaceutical)
(antiulcer agents; treatment of stasis ulcers with clopidogrel and dalteparin or clopidogrel alone)
IT Antiulcer agents
(decubitus ulcer inhibitors; treatment of stasis ulcers with clopidogrel and dalteparin or clopidogrel alone)
IT Vein
(insufficiency; treatment of stasis ulcers with clopidogrel and dalteparin or clopidogrel alone)
IT Anticoagulants
Blood coagulation
Wound healing
(treatment of stasis ulcers with clopidogrel and dalteparin or clopidogrel alone)
IT Blood vessel, disease
(vasculitis; treatment of stasis ulcers with clopidogrel and dalteparin or clopidogrel alone)
IT 9005-49-6, Dalteparin, biological studies 113665-84-2, Clopidogrel
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of stasis ulcers with clopidogrel and dalteparin or clopidogrel alone)

L41 ANSWER 24 OF 230 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 86194410 EMBASE
DN 1986194410
TI Cutaneouis manifestations associated with the presence of the lupus anticoagulant. A report of two cases and a review of the literature.
AU Grob J.-J.; Bonerandi J.-J.
CS Hopital Sainte Marguerite, 13277 Marseille Cedex 9, France
SO Journal of the American Academy of Dermatology, (1986) 15/2 I (211-219). CODEN: JAADDB
CY United States
DT Journal
FS 013 Dermatology and Venereology
025 Hematology
031 Arthritis and Rheumatism
026 Immunology, Serology and Transplantation
005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
LA English
AB Two patients with the lupus anticoagulant exhibited unusual cutaneous manifestations. They both fulfilled four criteria for systemic lupus erythematosus and had experienced deep **venous** thrombosis. The first patient suffered for a **leg ulcer** that resembled a pyoderma gangrenosum. The second patient presented erythematous and purplish macules on the fingertips. The histologic studies showed only microthrombosis in the dermal vessels without **vasculitis**, although such lesions in systemic lupus erythematosus are usually attributed to **vasculitis**. The association of these cutaneous lesions with lupus anticoagulant has never been reported. It is likely that this association is not fortuitous. After a review of the literature, it seems possible to individualize a new syndrome characterized by the presence of a subgroup of antiphospholipid antibodies. Thrombosis, spontaneous abortions, neurologic manifestations, pulmonary hypertension, positive results of a Coombs' test, and thrombocytopenia can be included in this syndrome, which overlaps with systemic lupus erythematosus. Certain cutaneous symptoms are associated with the presence of lupus anticoagulant or other antiphospholipid antibodies: **leg ulcers**, distal cutaneous ischemia, widespread cutaneous necrosis, and livedo. They can be considered as the dermatologic manifestations of this syndrome.
CT Medical Descriptors:
*deep vein thrombosis
*leg ulcer
*systemic lupus erythematosus
histopathology
skin defect
peripheral vascular system
priority journal
etiology
case report
human
Drug Descriptors:
*lupus anticoagulant

L23 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 1999:493072 CAPLUS
DN 131:309512
TI Differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing
AU Vaalamo, Maarit; Leivo, Tomi; Saarialho-Kere, Ulpu
CS Departments of Dermatology, Helsinki University Central Hospital and Central Military Hospital, and the Department of Anatomy, Institute of Biomedicine, University of Helsinki, Helsinki, Finland
SO Human Pathology (1999), 30(7), 795-802
CODEN: HPCQA4; ISSN: 0046-8177
PB W. B. Saunders Co.
DT Journal
LA English
CC 14-9 (Mammalian Pathological Biochemistry)
AB Wound healing is characterized by hemostasis, re-epithelialization, granulation tissue formation, and remodeling of the extracellular matrix. Matrix metalloproteinases and their specific inhibitors, TIMPs, contribute to these events. We investigated a total of 47 samples of normally healing wounds, chronic **venous ulcers**, **ulcerative vasculitis**, and suction blisters using immunohistochem. and in situ hybridization, to clarify the role of TIMPs in normal and aberrant wound repair. Expression of TIMP-1 and -3 mRNAs was found in proliferating keratinocytes in 3- to 5-day-old normally healing wounds, whereas no epidermal expression was detected in chronic **ulcers**. However, TIMP-3 protein was found in the proliferating epidermis in 20 of 24 samples representing both full-thickness acute and chronic wounds. TIMP-1 and TIMP-3 also were abundantly expressed by spindle-shaped, fibroblast-like, and plump, macrophage-like stromal cells, as well as by endothelial cells. In normally healing wounds, TIMP-2 protein localized under the migrating epithelial tip and to the stromal tissue under the eschar more frequently than in chronic ulcers. Occasional staining for TIMP-4 protein was detected in stromal cells of chronic ulcers near blood vessels. Our results indicate that TIMP-1 and TIMP-3 may be involved both in the regeneration of the epidermis by stabilizing the basement membrane zone and in the regulation of stromal remodeling and angiogenesis of the wound bed. Lack of TIMP-2 near the migrating epithelial wound edges might contribute to uncontrolled activity of MMP-2 in chronic ulcers. We conclude also that TIMPs are temporally and spatially tightly regulated and that the imbalance between metalloproteinases and TIMPs-1, -2, and -3 may lead to delayed wound healing.
ST metalloproteinases inhibitor TIMP skin wound healing
IT Gene, animal
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(TIMP-1; differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
IT Gene, animal
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(TIMP-3; differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
IT Gene, animal
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(TIMP-4; differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant

wound healing in humans)
IT Ulcer
(chronic venous; differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
IT Angiogenesis
Basement membrane
Blister
Blood vessel
Cell proliferation
Extracellular matrix
Wound healing
(differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
IT mRNA
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
IT Gene
(expression; differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
IT Skin
(keratinocyte; differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
IT Gene, animal
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(timp-2; differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
IT Blood vessel, disease
(vasculitis, ulcerative; differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
IT 124861-55-8, TIMP-2 140208-24-8, TIMP-1 145809-21-8, TIMP-3
186207-03-4, TIMP-4
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
IT 141907-41-7, Matrix metalloproteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing in humans)
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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L32 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS

AB Four cAMP-phosphodiesterases (PDE) belonging to families I, II, III and IV were identified in homogenates from human failing hearts. On fractionation of cardiac membranes, the cyclic GMP (cGMP)-inhibitable cAMP-PDE III copurified with the sarcoplasmic reticulum. The cAMP-PDE activities were sepd. from the sol. fraction by DEAE-ion exchange chromatog. and identified as belonging to the 4 different families of cAMP-PDEs. Various cAMP-PDE inhibitors, mostly cardiotonic compds., were tested for their inhibitory potency on the different cAMP-PDEs and their **selectivity** for the type III isoenzyme was detd. Isobutylmethyxanthine, papaverine, theophylline and **dipyridamole** inhibited PDE activity in a weak and nonselective manner. Milrinone, enoximone, adibendan, pimobendan, bemoradan and the newly synthesized R 81267 (I) and R 80122 (II) were selective PDE III inhibitors. However, the **IC50 values** on this enzyme varied from 10 .mu.M for enoximone to 0.036 .mu.M for II. The **selectivity** of the drugs for PDE III was calcd. by division of the **IC50 value** for PDE I, II or IV by the **IC50 value** for PDE III. PDE I/PDE III ratio ranged from 95 for enoximone to near 28,000 for II; the PDE II/PDE III ratios ranged from 95 for enoximone to 3,500 for II. Although there was strong variation between the drugs, most of them showed a high **selectivity** for PDE III in comparison to PDE I and to PDE II. In contrast, PDE IV appeared to be more sensitive to these substances. PDE IV/PDE III ratios ranging from 14 for milrinone to near 2,900 for II demonstrated this series of drugs to consist of minor and highly selective PDE-inhibitors. Inhibition kinetics for II of PDE III were detd. Ki Of II for PDE III was 0.007 .mu.M. In the same set of expts., Ki for cGMP and milrinone were 0.13 and 0.3 .mu.M. The cGMP and milrinone behave as competitive inhibitors whereas II showed a mixed type inhibition. Thus, within the series of cardiotonic drugs tested, major differences in inhibitory potency as well as in **selectivity** for PDE III are apparent. In view of putative compartmentalized occurrence of PDE III on the sarcoplasmic reticulum, the authors suggest that high isoenzyme **selectivity** might be required to evoke a selective PDE subtype inhibition within cardiac cells.

L32 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS

AB Four cAMP-phosphodiesterases (PDE) belonging to families I, II, III and IV were identified in homogenates from human failing hearts. On fractionation of cardiac membranes, the cyclic GMP (cGMP)-inhibitable cAMP-PDE III copurified with the sarcoplasmic reticulum. The cAMP-PDE activities were sepd. from the sol. fraction by DEAE-ion exchange chromatog. and identified as belonging to the 4 different families of cAMP-PDEs. Various cAMP-PDE inhibitors, mostly cardiotonic compds., were tested for their inhibitory potency on the different cAMP-PDEs and their **selectivity** for the type III isoenzyme was detd. Isobutylmethyxanthine, papaverine, theophylline and **dipyridamole** inhibited PDE activity in a weak and nonselective manner. Milrinone, enoximone, adibendan, pimobendan, bemoradan and the newly synthesized R 81267 (I) and R 80122 (II) were selective PDE III inhibitors. However, the **IC50 values** on this enzyme varied from 10 .mu.M for enoximone to 0.036 .mu.M for II. The **selectivity** of the drugs for PDE III was calcd. by division of the **IC50 value** for PDE I, II or IV by the **IC50 value** for PDE III. PDE I/PDE III ratio ranged from 95 for enoximone to near 28,000 for II; the PDE II/PDE III ratios ranged from 95 for enoximone to 3,500 for II. Although there was strong variation between the drugs, most of them showed a high **selectivity** for PDE III in comparison to PDE I and to PDE II. In contrast, PDE IV appeared to be more sensitive to these substances. PDE IV/PDE III ratios ranging from 14 for milrinone to near 2,900 for II demonstrated this series of drugs to consist of minor and highly selective PDE-inhibitors. Inhibition kinetics for II of PDE III were detd. Ki Of II for PDE III was 0.007 .mu.M. In the same set of expts., Ki for cGMP and milrinone were 0.13 and 0.3 .mu.M. The cGMP and milrinone behave as competitive inhibitors whereas II showed a mixed type inhibition. Thus, within the series of cardiotonic drugs tested, major differences in inhibitory potency as well as in **selectivity** for PDE III are apparent. In view of putative compartmentalized occurrence of PDE III on the sarcoplasmic reticulum, the authors suggest that high isoenzyme **selectivity** might be required to evoke a selective PDE subtype inhibition within cardiac cells.

L12 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2001:222911 CAPLUS
DN 135:15834
TI Characterization of human, dog and rabbit corpus cavernosum type 5 phosphodiesterases
AU Wang, Peng; Wu, Ping; Myers, Joyce G.; Stamford, Andrew; Egan, Robert W.; Billah, M. Motasim
CS Schering-Plough Research Institute, Kenilworth, NJ, 07033, USA
SO Life Sciences (2001), 68(17), 1977-1987
CODEN: LIFSAK; ISSN: 0024-3205
PB Elsevier Science Inc.
DT Journal
LA English
CC 7-2 (Enzymes)
Section cross-reference(s): 13
AB Human, dog and rabbit corpus cavernosum type 5 phosphodiesterases (**PDE5**) were isolated and their characteristics were compared. The three enzymes showed Km values of 0.8, 2.1 and 2.3 .mu.M, resp. They exhibited similar pH-dependence with optimal pH being 7.5. They required Mg2+ for activity and the activity was suppressed by high concns. of Zn2+ (0.1-1 mM). **Sildenafil** potently inhibited the three enzymes with **IC50** values of 3.6, 1.7 and 3.0 nM, resp. **Dipyridamole** and IBMX (3-isobutyl-1-methylxanthine) each also inhibited the three enzymes with similar, albeit lower, potencies (**IC50** about 1.1 and 5.7 .mu.M, resp.). However, zaprinast exhibited a significantly higher potency against the rabbit enzyme (**IC50** 53 nM) than against the human and dog **PDE5s** (**IC50** 332 and 217 nM, resp.). Thus, the corpus cavernosum **PDE5s** are very similar among the various species with the only significant difference being their sensitivity to zaprinast. Human platelet **PDE5** was also characterized by comparison with the corpus cavernosum enzyme. The platelet enzyme exhibited a Km, pH-, Mg2+ - and Zn2+-dependence, and sensitivity to **sildenafil** and zaprinast very similar to those of the corpus cavernosum **PDE5**. However, compared with corpus cavernosum **PDE5**, the platelet enzyme exhibited higher sensitivity to **dipyridamole** and IBMX (**IC50** 0.46 and 1.8 .mu.M, resp.). This study shows that despite similar kinetics and enzymic properties, corpus cavernosum **PDE5s** from different species, and corpus cavernosum and platelet **PDE5s**, can have differential sensitivity to pharmacol. inhibitors.
ST cGMP phosphodiesterase corpus cavernosum dog rabbit human
IT Penis
(corpus cavernosum; isolation and characterization of cGMP phosphodiesterase 5 from corpus cavernosum of human and dog and rabbit and comparison with human platelet enzyme)
IT Dog (Canis familiaris)
Platelet (blood)
Rabbit
(isolation and characterization of cGMP phosphodiesterase 5 from corpus cavernosum of human and dog and rabbit and comparison with human platelet enzyme)
IT Enzyme kinetics
Michaelis constant
(reaction kinetics of cGMP phosphodiesterase 5 from corpus cavernosum of human and dog and rabbit)
IT 58-32-2, **Dipyridamole** 28822-58-4, IBMX 37762-06-4, Zaprinast 139755-83-2, **Sildenafil**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor profile of cGMP phosphodiesterase 5 from corpus cavernosum of human and dog and rabbit and comparison with human platelet enzyme)
IT 9068-52-4P, CGMP phosphodiesterase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological

process); BSU (Biological study, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); PROC (Process)
(isoenzyme 5; isolation and characterization of cGMP phosphodiesterase 5 from corpus cavernosum of human and dog and rabbit and comparison with human platelet enzyme)

IT 7439-95-4, Magnesium, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(magnesium requirement of cGMP phosphodiesterase 5 from corpus cavernosum of human and dog and rabbit and comparison with human platelet enzyme)

IT 7440-66-6, Zinc, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(zinc inhibition of cGMP phosphodiesterase 5 from corpus cavernosum of human and dog and rabbit and comparison with human platelet enzyme)

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L20 ANSWER 5 OF 64 CAPLUS COPYRIGHT 2003 ACS
AB Human cAMP-specific phosphodiesterase (PDE7B), its cDNA, recombinant expression, use of primers or probes for gene detection, and use of antibodies for detection of its expression, are disclosed. We isolated a human cAMP-specific phosphodiesterase (PDE7B) cDNA from human caudate nucleus. The human PDE7B was composed of 450 amino acid residues with a mol. mass of 51,835 Da. The deduced amino acid sequence of human PDE7B was 64.1% identical to that of human PDE7A (67.1% identity in the catalytic region). Northern blot anal. demonstrated that PDE7B transcripts were abundantly expressed in the putamen, caudate nucleus, and heart followed by skeletal muscle, pancreas, and occipital pole. Recombinant PDE7B expressed in transfected COS-7 cells had a low cAMP Km value of 0.13 .mu.M, which is similar to the Km value of recombinant human PDE7A expressed in transfected COS-7 cells. Interestingly, the relative Vmax value of recombinant PDE7B was half to one-third of recombinant PDE7A. The PDE7B activity was inhibited by **dipyridamole** and SCH51866, with **IC50 values** of 1.1 .mu.M and 1.5 .mu.M, resp. Thus, the PDE7B exhibited unique tissue distribution in humans and kinetic profiles. Human PDE7B showed the lowest Km values compared to the other cAMP-hydrolyzing PDEs which have been reported to be expressed in the brain. Therefore, human PDE7B may be involved in the control of cAMP-mediated neural activity and cAMP metab. in the brain.
ST PDE7B cAMP specific phosphodiesterase human cDNA sequence; **dipyridamole** SCH51866 inhibition PDE7B kinetics COS cell expression
IT **58-32-2, Dipyridamole** 28822-58-4, IBMX 42971-09-5, Vinpocetine 150452-19-0, E4021 167298-74-0, SCH51866
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(PDE7B inhibition by; human cAMP-specific phosphodiesterase PDE7B)

L20 ANSWER 6 OF 64 CAPLUS COPYRIGHT 2003 ACS
AB A new cyclic nucleotide phosphodiesterase isoform PDE10A, recombinant expression, antibodies, and screening of ligands or regulators, are disclosed. Cloning Sf9 cells. CDNA encoding a novel phosphodiesterase (PDE) was isolated from a human fetal lung cDNA library and designated PDE10A. The deduced amino acid sequence contains 779 amino acids, including a putative cGMP binding sequence in the amino-terminal portion of the mol. and a catalytic domain that is 16-47% identical in amino acid sequence to those of other PDE families. Recombinant PDE10A transfected and expressed in COS-7 cells hydrolyzed cAMP and cGMP with Km values of 0.26 and 7.2 .mu.M, resp., and Vmax with cGMP was almost twice that with cAMP. Of the PDE inhibitors tested, **dipyridamole** was most effective, with **IC50 values** of 1.2 and 0.45 .mu.M for inhibition of cAMP and cGMP hydrolysis, resp. CGMP inhibited hydrolysis of cAMP, and cAMP inhibited cGMP hydrolysis with **IC50 values** of 14 and 0.39 .mu.M, resp. Thus, PDE10A exhibited properties of a cAMP PDE and a cAMP-inhibited cGMP PDE. PDE10A transcripts were particularly abundant in the putamen and caudate nucleus regions of brain and in thyroid and testis, and in much lower amts. in other tissues. The PDE10OA gene was located on chromosome 6q26 by fluorescent in situ hybridization anal. PDE10A represents a new member of the PDE superfamily, exhibiting unique kinetic properties and inhibitor sensitivity.
IT **58-32-2, Dipyridamole**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(PDE10A inhibition by; human cyclic nucleotide phosphodiesterase that hydrolyzes both cAMP and cGMP (PDE10A))

L20 ANSWER 7 OF 64 CAPLUS COPYRIGHT 2003 ACS
AB This study reports the identification and characterization of a cAMP-specific phosphodiesterase from the parasitic hemoflagellate

L20 ANSWER 8 OF 64 CAPLUS COPYRIGHT 2003 ACS

AB Human, dog and rabbit corpus cavernosum type 5 phosphodiesterases (PDE5) were isolated and their characteristics were compared. The three enzymes showed Km values of 0.8, 2.1 and 2.3 .mu.M, resp. They exhibited similar pH-dependence with optimal pH being 7.5. They required Mg2+ for activity and the activity was suppressed by high concns. of Zn2+ (0.1-1 mM). Sildenafil potently inhibited the three enzymes with **IC50 values** of 3.6, 1.7 and 3.0 nM, resp. **Dipyridamole** and IBMX (3-isobutyl-1-methylxanthine) each also inhibited the three enzymes with similar, albeit lower, potencies (IC50 about 1.1 and 5.7 .mu.M, resp.). However, zaprinast exhibited a significantly higher potency against the rabbit enzyme (IC50 53 nM) than against the human and dog PDE5s (IC50 332 and 217 nM, resp.). Thus, the corpus cavernosum PDE5s are very similar among the various species with the only significant difference being their sensitivity to zaprinast. Human platelet PDE5 was also characterized by comparison with the corpus cavernosum enzyme. The platelet enzyme exhibited a Km, pH-, Mg2+ - and Zn2+-dependence, and sensitivity to sildenafil and zaprinast very similar to those of the corpus cavernosum PDE5. However, compared with corpus cavernosum PDE5, the platelet enzyme exhibited higher sensitivity to **dipyridamole** and IBMX (IC50 0.46 and 1.8 .mu.M, resp.). This study shows that despite similar kinetics and enzymic properties, corpus cavernosum PDE5s from different species, and corpus cavernosum and platelet PDE5s, can have differential sensitivity to pharmacol. inhibitors.

IT **58-32-2**, **Dipyridamole** 28822-58-4, IBMX 37762-06-4, Zaprinast 139755-83-2, Sildenafil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor profile of cGMP phosphodiesterase 5 from corpus cavernosum of human and dog and rabbit and comparison with human platelet enzyme)

L20 ANSWER 10 OF 64 CAPLUS COPYRIGHT 2003 ACS

AB Phosphodiesterase 11A (PDE11A) is a recently identified family of cAMP and cGMP hydrolyzing enzymes. Thus far, a single splice variant designated as PDE11A1 has been reported. In this study, we identify and characterize two addnl. splice variants of PDE11A, PDE11A2 and PDE11A3. The full-length cDNAs are 2,141 bp for PDE11A2 and 2205 bp for PDE11A3. The ORF of PDE11A2 predicts a protein of 576 aa with a mol. mass of 65.8 kDa. The ORF of PDE11A3 predicts a protein of 684 aa with a mol. mass of 78.1 kDa. Comparison of the PDE11A2 sequence with that of PDE11A1 indicates an addnl. 86 aa at the N terminus of PDE11A2. Part of this sequence extends the potential cGMP binding region (GAF domain) present in PDE11A1. Compared with PDE11A2, PDE11A3 has an addnl. 108 N-terminal amino acids. Sequence anal. of PDE11A3 indicates the presence of another GAF domain in this region. This diversification of regulatory sequences in the N-terminal region of PDE11A splice variants suggests the interesting possibility of differential regulation of these enzymes. Recombinant PDE11A2 and -A3 proteins expressed in the Baculovirus expression system have the ability to hydrolyze both cAMP and cGMP. The Km values for cAMP hydrolysis are 3.3 .mu.M and 5.7 .mu.M for PDE11A2 and PDE11A3, resp. The Km values for cGMP hydrolysis are 3.7 .mu.M and 4.2 .mu.M for PDE11A2 and PDE11A3, resp. Both PDEs showed a Vmax ratio for cAMP/cGMP of approx. 1.0. PDE11A2 is sensitive to **dipyridamole**, with an IC50 of 1.8 .mu.M, and to zaprinast, with an IC50 of 28 .mu.M. PDE11A3 demonstrated similar pattern of inhibitor sensitivity with **IC50 values** of 0.82 and 5 .mu.M for **dipyridamole** and zaprinast, resp.

IT **58-32-2**, **Dipyridamole** 37762-06-4, Zaprinast
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cloning and characterization of two splice variants of human phosphodiesterase 11A)

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L21 ANSWER 7 OF 69 CAPLUS COPYRIGHT 2003 ACS
AN 2003:4158 CAPLUS
TI MDR1-mediated interaction of digoxin with antiarrhythmic or antianginal drugs
AU Kakumoto, Mikio; Takara, Kohji; Sakaeda, Toshiyuki; Tanigawara, Yusuke; Kita, Tomoko; Okumura, Katsuhiko
CS Department of Hospital Pharmacy, School of Medicine, Kobe University, Kobe, 650-0017, Japan
SO Biological & Pharmaceutical Bulletin (2002), 25(12), 1604-1607
CODEN: BPBLEO; ISSN: 0918-6158
PB Pharmaceutical Society of Japan
DT Journal
LA English
CC 1 (Pharmacology)
AB The multidrug transporter, MDR1-mediated interaction of digoxin with antiarrhythmic or antianginal drugs was examd. in vitro by using the MDR1-overexpressing LLC-GA5-COL150 cells, which were established by transfection with human MDR1 cDNA into porcine kidney epithelial LLC-PK1 cells. Amiodarone, its active metabolite monodesethyl-amiodarone (DEA), and quinidine markedly inhibited the basal-to-apical transport (renal secretion) of [3H]digoxin and increased the apical-to-basal transport (reabsorption), but cibenzoline and lidocaine showed slight inhibition of the transport, and disopyramide and mexiletin had no such effects. The **IC50 values** for amiodarone, DEA and quinidine on [3H]digoxin transport in LLC-GA5-COL150 cells were 5.48 .mu.M, 1.27 .mu.M and 9.52 .mu.M, resp. These were comparable to, or only several times the achievable concn. in clin. use, suggesting that MDR1 could be responsible for the drug interaction between digoxin and amiodarone found in clin. reports and that DEA contributes the elevation of digoxin serum concn. Similarly, **dipyridamole** altered the transport, but isosorbide showed only slight modification of the transport. The **IC50 value** for **dipyridamole** was 40.0 .mu.M, also only several times the achievable concn. in clin. use, indicating a risk of interaction.

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L57 ANSWER 74 OF 74 USPATFULL

ACCESSION NUMBER:	2002:8489 USPATFULL		
TITLE:	Retinoid receptor interacting polynucleotides, polypeptides, and antibodies		
INVENTOR(S):	Shi, Yanggu, Gaithersburg, MD, UNITED STATES Ruben, Steven M., Olney, MD, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002004489	A1	20020110
APPLICATION INFO.:	US 2001-788600	A1	20010221 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. WO 2000-US22351, filed on 15 Aug 2000, UNKNOWN		
	NUMBER	DATE	
PRIORITY INFORMATION:	US 1999-148757P	19990816 (60)	
	US 2000-189026P	20000314 (60)	
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850		
NUMBER OF CLAIMS:	22		
EXEMPLARY CLAIM:	1		
LINE COUNT:	11257		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L6 ANSWER 4 OF 6 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 87074827 EMBASE
DN 1987074827
TI **Venous leg ulcers**. The post-phlebitic syndrome.
AU Heng M.C.Y.
CS Division of Dermatology, Department of Medicine, UCLA School of Medicine, Sepulveda, CA 91343, United States
SO International Journal of Dermatology, (1987) 26/1 (14-21).
CODEN: IJDEBB
CY United States
DT Journal
FS 037 Drug Literature Index
013 Dermatology and Venereology
020 Gerontology and Geriatrics
LA English
CT Medical Descriptors:
***leg ulcer**
*drug therapy
*vein thrombosis
management
pathophysiology
review
priority journal
therapy
topical drug administration
short survey
human
diagnosis
clinical article
peripheral vascular system
Drug Descriptors:
*acetylsalicylic acid
*benzoyl peroxide
***dipyridamole**
RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (benzoyl peroxide) 94-36-0; (**dipyridamole**) 58-32-2
CN Aspirin

L6 ANSWER 5 OF 6 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 85056970 EMBASE
DN 1985056970
TI [On history of **venous** drugs].
ZUR GESCHICHTE DER VENENPHARMAKA.
AU Schneider W.
CS Univ. Hautklinik, D 7400 Tubingen, Germany
SO Phlebologie und Proktologie, (1984) 13/3 (183-186).
CODEN: PHPRD5
CY Germany
DT Journal
FS 037 Drug Literature Index
030 Pharmacology
LA German
SL English; French
CT Medical Descriptors:
*chromone
***leg ulcer**
*drug therapy
*phlebitis
*vein thrombosis
peripheral vascular system
therapy
short survey

human
Drug Descriptors:
*acetylsalicylic acid
*anticoagulant agent
*asasantin
*benzarone
*bromocriptine mesilate
*dicoumarol
*dihydroergotamine
*dihydroergotoxine mesilate
***dipyridamole**
*diuretic agent
*ergotamine tartrate
*escin
*fibrinolytic agent
*flavonoid
*furosemide
*heparin
*heparinoid
*hirudin
*methylergometrine tartrate
*methysergide
*streptokinase
*sulfinpyrazone
*urokinase
dihydroergotamine mesilate
methylergometrine maleate

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (benzarone) 1477-19-6; (bromocriptine mesilate) 22260-51-1; (dicoumarol) 66-76-2; (dihydroergotamine) 511-12-6; (dihydroergotoxine mesilate) 8067-24-1; (**dipyridamole**) 58-32-2; (ergotamine tartrate) 379-79-3; (escin) 6805-41-0, 8067-31-0; (furosemide) 54-31-9; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (hirudin) 8001-27-2; (methylergometrine tartrate) 57774-31-9; (methysergide) 16509-15-2, 361-37-5, 62288-72-6; (streptokinase) 9002-01-1; (sulfinpyrazone) 57-96-5; (urokinase) 139639-24-0; (dihydroergotamine mesilate) 6190-39-2; (methylergometrine maleate) 57432-61-8

CN Colfarit; Asasantin; Anturane; Gynergen; Pravidel; Dihydergot; Hydergin; Methergin; Deseril; Fragivix

L6 ANSWER 6 OF 6 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 75200482 EMBASE
DN 1975200482
TI Deep vein thrombosis: detection and prevention.
AU Kakkar V.V.
CS Dept. Surg., King's Coll. Hosp. Med. Sch., London, United States
SO Circulation, (1975) 51/1 (8-19).
CODEN: CIRCAZ
DT Journal
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
009 Surgery
033 Orthopedic Surgery
LA English
AB **Venous** thrombosis and pulmonary embolism are serious hazards after surgery and trauma, in childbirth, and in a variety of medical conditions, including cardiac failure and infarction. It has been estimated that approximately 21,000 patients die each year from this cause in the United Kingdom; the figures for the United States range between 47,000 and 142,000. Apart from the immediate risk to life, one must also consider the late sequelae of this disease: swelling of the **legs**, varicose veins, **ulceration**, and other trophic changes which represent an equally distressing condition. Recently there has also been a greater awareness of the ubiquity of thromboembolic disease and of the possibility that there is an absolute as well as a relative increase in

its occurrence. The deaths recorded in the Registrar General's Report for England and Wales between 1943 and 1959 indicate that there has been an almost sixfold increase in mortality due to pulmonary embolism during this period. These findings clearly indicate that if this 'epidemic' of deaths from pulmonary embolism is to be effectively controlled then the disease must be detected at an early stage when treatment may be effective or, an even better approach, a simple method of prophylaxis which is successful in the total elimination of this condition should be investigated. The recent developments that have taken place in the field of detection and prevention of **venous** thromboembolism are reviewed very briefly in this paper.

CT Medical Descriptors:
*deep vein thrombosis
*embolism
*fibrinogen i 125
*lung embolism
*orthopedic surgery
*phlebography
*plethysmography
*thrombosis
*thrombosis prevention
*ultrasound
*vein thrombosis
diagnosis
major clinical study
therapy
Drug Descriptors:
*acetylsalicylic acid
*anticoagulant agent
*dextran
*dextran 70
***dipyridamole**
*ethylestrenol
*fibrinogen
*heparin
*iodine 125
*phenformin

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dextran) 87915-38-6, 9014-78-2; (**dipyridamole**) 58-32-2; (ethylestrenol) 965-90-2; (fibrinogen) 9001-32-5; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (iodine 125) 14158-31-7, 22822-81-7; (phenformin) 114-86-3, 834-28-6

=>

L6 ANSWER 1 OF 6 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001396086 EMBASE
TI **Leg ulcer** diagnosis and management.
AU Choucair M.M.; Fivenson D.P.
CS Dr. D.P. Fivenson, Department of Dermatology, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI 48202, United States. dfivens1@hfhs.org
SO Dermatologic Clinics, (2001) 19/4 (659-678).
Refs: 97
ISSN: 0733-8635 CODEN: DRMCDJ
CY United States
DT Journal; General Review
FS 006 Internal Medicine
013 Dermatology and Venereology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Lower extremity **ulcers** can be challenging diagnostically and therapeutically. This article provides an overview of the different kinds of lower extremity wounds typically seen by the medical dermatologist. It also reviews new treatment modalities, including topical growth factors and bioengineered skin. A team approach is emphasized.
CT Medical Descriptors:
***leg ulcer: CO, complication**
***leg ulcer: DI, diagnosis**
***leg ulcer: DT, drug therapy**
***leg ulcer: TH, therapy**
diagnostic approach route
teamwork
treatment planning
Raynaud phenomenon: DI, diagnosis
Raynaud phenomenon: ET, etiology
pathogenesis
peripheral occlusive artery disease: DI, diagnosis
peripheral occlusive artery disease: DT, drug therapy
peripheral occlusive artery disease: TH, therapy
wound care
oxygen therapy
Buerger disease: DI, diagnosis
artery embolism
artery thrombosis
livedo reticularis: DI, diagnosis
livedo reticularis: DT, drug therapy
vasculitis: DI, diagnosis
calcinosis: DT, drug therapy
calcinosis: TH, therapy
drug induced disease: SI, side effect
vein insufficiency
venous stasis: DT, drug therapy
venous stasis: TH, therapy
ulcer: TH, therapy
pyoderma gangrenosum: DI, diagnosis
pyoderma gangrenosum: DT, drug therapy
human
review
priority journal
Drug Descriptors:
pentoxifylline: DT, drug therapy
clopidogrel: DT, drug therapy
cilostazol: DT, drug therapy
analgesic agent: DT, drug therapy
antithrombocytic agent: DT, drug therapy
acetylsalicylic acid: DT, drug therapy
fibrinolytic agent: DT, drug therapy

stanozolol: DT, drug therapy
corticosteroid: AD, drug administration
corticosteroid: DT, drug therapy
corticosteroid: IL, intralesional drug administration
corticosteroid: IV, intravenous drug administration
corticosteroid: PO, oral drug administration
corticosteroid: TP, topical drug administration
immunosuppressive agent: DT, drug therapy
antimalarial agent: DT, drug therapy
tumor necrosis factor alpha blocking agent: DT, drug therapy
immunomodulating agent: DT, drug therapy
dipyridamole: DT, drug therapy
ticlopidine: DT, drug therapy
phosphate binding agent: DT, drug therapy
vitamin D
chlorpromazine: AE, adverse drug reaction
hydralazine: AE, adverse drug reaction
procainamide: AE, adverse drug reaction
antibiotic agent: DT, drug therapy
antibiotic agent: TP, topical drug administration
benzoyl peroxide: DT, drug therapy
cromoglycate disodium: DT, drug therapy
cromoglycate disodium: TP, topical drug administration
granulocyte macrophage colony stimulating factor: DT, drug therapy
granulocyte macrophage colony stimulating factor: IL, intralesional drug administration
tsukubaenolide: DT, drug therapy
tsukubaenolide: TP, topical drug administration
macrolide: DT, drug therapy
methylprednisolone: DT, drug therapy
methylprednisolone: IV, intravenous drug administration
dapsone: DT, drug therapy
minocycline: DT, drug therapy
unindexed drug
unclassified drug

RN (pentoxifylline) 6493-05-6; (clopidogrel) 113665-84-2, 120202-66-6, 90055-48-4, 94188-84-8; (cilostazol) 73963-72-1; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (stanozolol) 10418-03-8, 302-96-5; (**dipyridamole**) 58-32-2; (ticlopidine) 53885-35-1, 55142-85-3; (chlorpromazine) 50-53-3, 69-09-0; (hydralazine) 304-20-1, 86-54-4; (procainamide) 51-06-9, 614-39-1; (benzoyl peroxide) 94-36-0; (cromoglycate disodium) 15826-37-6, 16110-51-3, 93356-79-7, 93356-84-4; (tsukubaenolide) 104987-11-3; (methylprednisolone) 6923-42-8, 83-43-2; (dapsone) 80-08-0; (minocycline) 10118-90-8, 11006-27-2, 13614-98-7
CN Fk 506

L6 ANSWER 2 OF 6 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 93043858 EMBASE
DN 1993043858
TI **Ulcerating** necrobiosis lipoidica effectively treated with pentoxifylline.
AU Noz K.C.; Korstanje M.J.; Vermeer B.J.
CS Department of Dermatology, Academic Hospital, Rijnsburgerweg 10,2333 AA Leiden, Netherlands
SO Clinical and Experimental Dermatology, (1993) 18/1 (78-79).
ISSN: 0307-6938 CODEN: CEDEDE
CY United Kingdom
DT Journal; Article
FS 013 Dermatology and Venereology
037 Drug Literature Index
LA English
SL English
AB A 30-year-old man had suffered from persistent **ulceration** within

an area of necrobiosis lipoidica diabeticorum for 13 months. The **ulcerating** necrobiosis lipoidica was resistant to topical therapy and oral therapy with acetylsalicylic acid. However, the **ulcers** healed completely within 8 weeks of administration of 400 mg pentoxifylline twice daily. Necrobiosis lipoidica has a unique diagnostic appearance. The clinical features, histopathology, pathogenesis and treatment are discussed extensively by Lowitt et al. The treatment of **ulcerating** necrobiosis lipoidica is difficult. Attempts have been made, with varying results, to treat necrobiosis lipoidica with topical corticosteroids, fibrinolytics and antiplatelet agents, e.g. acetylsalicyclic acid and **dipyridamole**, either alone or in combination. As pentoxifylline is effective in healing **venous ulcers** of the **leg** we decided to try this drug for the treatment of **ulcerating** necrobiosis lipoidica.

CT Medical Descriptors:
*insulin dependent diabetes mellitus
***skin ulcer: DT, drug therapy**
***skin ulcer: CO, complication**
adult
article
case report
human
male
oral drug administration
priority journal
topical drug administration
Drug Descriptors:
*acetylsalicylic acid: DT, drug therapy
*pentoxifylline: DT, drug therapy

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (pentoxifylline) 6493-05-6

L6 ANSWER 3 OF 6 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 91303617 EMBASE
DN 1991303617
TI Antiphospholipid syndrome and cutaneous vasoocclusive disorders.
AU Grattan C.E.H.; Burton J.L.
CS Department of Dermatology, Norfolk and Norwich Hospital, Brunswick Rd,Norwich, United Kingdom
SO Seminars in Dermatology, (1991) 10/3 (152-159).
ISSN: 0278-145X CODEN: SDERDN
CY United States
DT Journal; Article
FS 013 Dermatology and Venereology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB The antiphospholipid syndrome (characterized by the presence of circulating lupus anticoagulants or anticardiolipin antibodies) was first recognized in patients with systemic lupus erythematosus (SLE), but the syndrome can also exist in the absence of SLE. The clinical features include arterial or **venous** thrombosis, recurrent abortion, neurological problems, and various cutaneous disorders including thrombophlebitis, livedo reticularis, atrophie blanche, **leg ulcers**, and gangrene. In some cases, antiphospholipid antibodies may play a role with other recognized syndromes characterized by vascular occlusion, such as Sneddon's syndrome (livedo reticularis with cerebrovascular occlusion) and Degos' disease.

CT Medical Descriptors:
*skin blood vessel disorder
*skin necrosis: CO, complication
*thrombosis: PC, prevention
*thrombosis: CO, complication

antiphospholipid syndrome: DI, diagnosis
antiphospholipid syndrome: DT, drug therapy
article
blood vessel occlusion: CO, complication
human
immunosuppressive treatment
priority journal
systemic lupus erythematosus: DT, drug therapy
Drug Descriptors:
*anticoagulant agent: DT, drug therapy
*cardiolipin antibody: EC, endogenous compound
*lupus anticoagulant: EC, endogenous compound
*phenothiazine: DT, drug therapy
*phospholipid antibody: EC, endogenous compound
*procainamide: DT, drug therapy
acetylsalicylic acid: DT, drug therapy
acetylsalicylic acid: CB, drug combination
dipyridamole: DT, drug therapy
dipyridamole: CB, drug combination
prednisolone: DT, drug therapy
RN (phenothiazine) 92-84-2; (procainamide) 51-06-9, 614-39-1; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (**dipyridamole**) 58-32-2; (prednisolone) 50-24-8

AB Forty-one patients with ischemic heart disease (IHD) of the age 60 .+-. 12.3 years were hospitalized and **treated** two weeks with Curantyl (**Dipyridamole**) which was applied per os in a dose of 75 mg 3 times, and after another two weeks 34 of them were applied Isoptin (Verapamil) in a dose of 40 mg 3 times daily. The head conductivity (J.cntdot.m-1, sec-1.cntdot..degree.C.gtoreq.10-2, HC) and skin temperature (.degree.C, ST) were examined at the isothermic level 2 cm above the inner ankle by the apparatus Fluvograph 2 of Hartmann and Braun A.G. (BRD). The HC after Isoptin application above the left and right ankle was in 34 patients increased significantly ($p < 0.001$). In patients with IHD after Curantyl application the HC and ST was significantly decreased above the left and right ankle in 9 (21.9%) and in 12 (30.3%), respectively. Curantyl could deteriorate HC and so worsen legs **ulceration** healing and to point up ischemia in patients with associated chronic postphlebitis syndrome with **ulcera** crurium.

ACCESSION NUMBER: 91157199 EMBASE
DOCUMENT NUMBER: 1991157199
TITLE: Heat conductivity and skin temperature at the treatment of ischemic heart disease with curantyl and isoptin.
AUTHOR: Kollar J.; Uhrik J.; Hejj F.
CORPORATE SOURCE: Institute of Experimental Medicine, University P.J. Safarik, Kosice, Czechoslovakia
SOURCE: International Angiology, (1991) 10/1 (34-37).
ISSN: 0392-9590 CODEN: INANEK
COUNTRY: Italy
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L84 ANSWER 30 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AB Six patients with no hemodynamically significant atherosclerotic lesions of the lower limb arteries but with ischemic changes of the feet or toes were studied and diagnosed as having atherothrombotic microembolism. All patients were non claudicators and had peripheral Doppler examinations on admission. Five patients experienced more than one separate episode of microembolization involving both extremities. None presented with a history of heart disease or diabetes. Biplanar arteriograms revealed in every case atherosclerotic degeneration of the aorta without any obstructing lesions and anatomical arterial continuity between the aorta and the site of distal embolization. Three patients who refused operation, were **treated** conservatively, with a combination of **dipyridamole** plus aspirin. Three other patients had surgical repair of their atheromatous infrarenal aorta: in two cases thromboendarterectomy was performed, and in the other a Dacron bifurcated graft interposition. No amputations resulted in the patients **treated** medically, but one of the surgical group lost one toe. This study confirms that atherothrombotic microembolism from an **ulcerated** atherosclerotic aorta is a potential threat to the extremities and indicates that the optimal therapy for this syndrome has yet to be found.

ACCESSION NUMBER: 90271981 EMBASE
DOCUMENT NUMBER: 1990271981
TITLE: Atherothrombotic microembolism of the lower extremities (the blue toe syndrome) from atherosclerotic non-aneurysmal aortic plaques.
AUTHOR: Benvegna S.; Cassina I.; Giuntini G.; Rusignuolo F.; Talarico F.; Florena M.
CORPORATE SOURCE: Dipartimento di Discipline Chirurgiche ed Anatomiche, Cattedra di Patologia Chirurgica ''R'', Universita degli Studi di Palermo, Palermo, Italy
SOURCE: Journal of Cardiovascular Surgery, (1990) 31/1 (87-91). ISSN: 0021-9509 CODEN: JCVSA2
COUNTRY: Italy
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English

L84 ANSWER 28 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AB A 30-year-old man had suffered from persistent **ulceration** within an area of necrobiosis lipoidica diabeticorum for 13 months. The **ulcerating** necrobiosis lipoidica was resistant to topical therapy and oral therapy with acetylsalicylic acid. However, the **ulcers** healed completely within 8 weeks of administration of 400 mg pentoxifylline twice daily. Necrobiosis lipoidica has a unique diagnostic appearance. The clinical features, histopathology, pathogenesis and **treatment** are discussed extensively by Lowitt et al. The **treatment** of **ulcerating** necrobiosis lipoidica is difficult. Attempts have been made, with varying results, to **treat** necrobiosis lipoidica with topical corticosteroids, fibrinolytics and antiplatelet agents, e.g. acetylsalicyclic acid and **dipyridamole**, either alone or in combination. As pentoxifylline is effective in healing venous **ulcers** of the leg we decided to try this drug for the **treatment** of **ulcerating** necrobiosis lipoidica.

ACCESSION NUMBER: 93043858 EMBASE
DOCUMENT NUMBER: 1993043858
TITLE: Ulcerating necrobiosis lipoidica effectively treated with pentoxifylline.
AUTHOR: Noz K.C.; Korstanje M.J.; Vermeer B.J.
CORPORATE SOURCE: Department of Dermatology, Academic Hospital, Rijnsburgerweg 10,2333 AA Leiden, Netherlands
SOURCE: Clinical and Experimental Dermatology, (1993) 18/1 (78-79). ISSN: 0307-6938 CODEN: CEDEDE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L97 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 2000:144772 CAPLUS
DN 132:189689
TI Bioreductive conjugates for drug targeting
IN Adams, Ged; Blake, David; Naughton, Declan; Stratford, Ian
PA Theramark Limited, UK; Adams, Margaret
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K047-48
CC 1-12 (Pharmacology)
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000010610	A2	20000302	WO 1999-GB2606	19990819
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9954296	A1	20000314	AU 1999-54296	19990819
PRAI	GB 1998-18027	A	19980819		
	GB 1998-18156	A	19980820		
	WO 1999-GB2606	W	19990819		

OS MARPAT 132:189689
AB The use of a bioreductive conjugate comprised of a noncytotoxic bioreductive moiety having linked thereto at least one therapeutic agent, and salts thereof, is disclosed for the healing of **wounds** and the treatment of fibrotic disorders, **ulcerative** colitis, inflammatory bowel disease, epilepsy, cardiovascular reperfusion injury, cerebral reperfusion injury, hypertension, cystic fibrosis, psoriasis, para-psoriasis, peptic **ulcers**, gastric **ulcers**, duodenal **ulcers**, diabetic **ulcers** dementia, oncol., AIDS, rheumatoid arthritis, diabetes, and ischemia. Various specific conjugates for treating these conditions are also disclosed.
ST bioreductive conjugate drug targeting therapeutic
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TGF.beta.3; bioreductive conjugates for drug targeting)
IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alkylation; bioreductive conjugates for drug targeting)
IT Psoriasis
(and para-psoriasis; bioreductive conjugates for drug targeting)
IT Mitosis
(antimitotics; bioreductive conjugates for drug targeting)
IT Actins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(assembly and organization modulators; bioreductive conjugates for drug targeting)
IT Alkylation
(biochem.; bioreductive conjugates for drug targeting)
IT Anti-AIDS agents
Anti-inflammatory agents
Anti-ischemic agents
Anticoagulants
Anticonvulsants

Antidiabetic agents
Antihypertensives
Antirheumatic agents
Antitumor agents
Antiulcer agents
Apoptosis
Cardiovascular agents
Cystic fibrosis
Drug metabolism
Drug targeting
Fibrinolytics
Fibrosis
Hypoxia, animal
Immunomodulators
Immunosuppressants
Platelet aggregation inhibitors
Radical scavengers
Vasodilators
Wound healing promoters
(bioreductive conjugates for drug targeting)

IT Interleukin 10
Interleukin 4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bioreductive conjugates for drug targeting)

IT Interleukin 1
Platelet-derived growth factors
Sex hormones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(bioreductive conjugates for drug targeting)

IT Ion channel blockers
(calcium; bioreductive conjugates for drug targeting)

IT Drugs
(conjugates; bioreductive conjugates for drug targeting)

IT Corticosteroids, biological studies
Steroids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates; bioreductive conjugates for drug targeting)

IT Diabetes mellitus
(diabetic **ulcer**; bioreductive conjugates for drug targeting)

IT Cell cycle
(drugs specific for; bioreductive conjugates for drug targeting)

IT Intestine, disease
(duodenum, **ulcer**; bioreductive conjugates for drug targeting)

IT Growth factors, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(growth factor neutralizing agents; bioreductive conjugates for drug targeting)

IT Intestine, disease
(inflammatory; bioreductive conjugates for drug targeting)

IT Lung, neoplasm
Lung, neoplasm
(inhibitors, A549; bioreductive conjugates for drug targeting)

IT Interleukin 6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; bioreductive conjugates for drug targeting)

IT Reperfusion
(injury, including cerebral reperfusion injury; bioreductive conjugates for drug targeting)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(integrin receptor activation inhibitors; bioreductive conjugates for drug targeting)

IT Antitumor agents
Antitumor agents
(lung, A549; bioreductive conjugates for drug targeting)

IT **Ulcer**
(peptic; bioreductive conjugates for drug targeting)

IT Stomach, disease
(**ulcer**; bioreductive conjugates for drug targeting)

IT Intestine, disease
(**ulcerative** colitis; bioreductive conjugates for drug targeting)

IT Proteins, general, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**wound** site, growth factor-assocd.; bioreductive conjugates for drug targeting)

IT Adrenoceptor antagonists
(.beta.-; bioreductive conjugates for drug targeting)

IT Polysaccharides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-glycans, sol.; bioreductive conjugates for drug targeting)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.1-; bioreductive conjugates for drug targeting)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.2-; bioreductive conjugates for drug targeting)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.gamma.; bioreductive conjugates for drug targeting)

IT 114560-25-7 114560-34-8, EO 8 161518-24-7, RB 94547J
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bioreductive conjugates for drug targeting)

IT 50-06-6D, Phenobarbitone, conjugates, biological studies 50-24-8D, Prednisolone, conjugates 50-78-2D, Aspirin, conjugates 52-53-9D, Verapamil, conjugates 52-67-5D, Penicillamine, conjugates 53-86-1D, Indomethacin, conjugates 57-41-0D, Phenytoin, conjugates **58-32-2D**, Dipyridamole, conjugates 59-05-2D, Methotrexate, conjugates 66-97-7D, Psoralen, conjugates 89-57-6D, Mesalazine, conjugates 89-57-6D, 5-Aminosalicylic acid, derivs., conjugates 118-42-3D, Hydroxychloroquine, conjugates 305-03-3D, Chlorambucil, conjugates 443-48-1D, Metronidazole, conjugates 446-86-6D, Azathioprine, conjugates 599-79-1D, Sulfasalazine, conjugates 1069-66-5D, Sodium valproate, conjugates 1406-16-2D, Vitamin D, analogs, conjugates 6556-11-2D, Inositol nicotinate, conjugates 12244-57-4D, Myochrysine, conjugates 15307-86-5D, Diclofenac, conjugates 15687-27-1D, Ibuprofen, conjugates 21829-25-4D, Niphedipine, conjugates 22204-53-1D, Naproxen, conjugates 26171-23-3D, Tolmetin, conjugates 29679-58-1D, Fenoprofen, conjugates 38194-50-2D, Sulindac, conjugates 51234-28-7D, Benoxaprofen, conjugates 56180-94-0D, Acarbose, conjugates 59865-13-3D, Cyclosporin A, conjugates 62571-86-2D, Captopril, conjugates 67763-97-7D, Insulin-like growth factor II, conjugates 73590-58-6D, Omeprazole, conjugates 79217-60-0D, Cyclosporin, derivs., conjugates 87333-19-5D, Ramipril, conjugates 87679-37-6D, Trandolapril, conjugates 97240-79-4D, Topiramate, conjugates 103577-45-3D, Lansoprazole, conjugates 113194-81-3, TMK 209 117976-89-3D, Rabeprazole, conjugates 259876-40-9, TMK 210 259876-41-0, TMK 207
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); **BIOL (Biological**

study); USES (Uses)
(bioreductive conjugates for drug targeting)

IT 106096-92-8, Acidic fibroblast growth factor 106096-93-9, Basic fibroblast growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(bioreductive conjugates for drug targeting)

IT 9015-82-1, Angiotensin-converting enzyme 9025-82-5, **Phosphodiesterase** 9036-21-9, **Phosphodiesterase** IV 9055-65-6, Prostaglandin synthetase 9068-52-4, **Phosphodiesterase** V 81669-70-7, Metalloprotease 99676-46-7, Kexin 125978-95-2, Nitric oxide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; bioreductive conjugates for drug targeting)

IT 57285-09-3, Inhibin 114949-22-3, Activin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(stimulators; bioreductive conjugates for drug targeting)

=>

L40 ANSWER 17 OF 90 USPATFULL

SUMM In summary, the biochemical, physiological, and clinical effects of **PDE5** inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, **inflammatory**, and/or endocrine function is desirable. The compounds of formula (I), therefore, have utility in the **treatment** of a number of disorders, including stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, acute respiratory distress syndrome, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., postpercutaneous transluminal coronary or carotid angioplasty, or post-bypass surgery graft stenosis), peripheral vascular disease, vascular disorders, such as Raynaud's disease, thrombocythemia, **inflammatory** diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic **ulcer**, osteoporosis, preterm labor, benign prostatic hypertrophy, male and female erectile dysfunction, and diseases characterized by disorders of gut motility (e.g., irritable bowel syndrome or IBS).

SUMM The present selective **PDE5** inhibitors in combination with **vasodilators**, including nitric oxide and nitric oxide donators and precursors, such as the organic nitrate **vasodilators** which act by releasing nitric oxide in vivo, are especially useful in treatment of angina, congestive heart failure, and malignant hypertension (e.g., pheochromocytoma). Related to the capacity of the present **PDE5** inhibitors to potentiate nitric oxide donors and precursors is their ability, in spontaneously hypertensive rats, to reverse the desensitization to these agents that occurs with chronic use.

SUMM Alpha-adrenergic blockers inhibit vasoconstriction in the corpus cavernosum. Because **PDE5** inhibitors enhance **vasodilation** of the same smooth muscle tissue, a **PDE5** inhibitor of formula (I) and an 60 -adrenergic blocker, like phentolamine or prazocin, or a centrally acting dopaminergic agent, like apomorphine, can be expected to potentiate one another in a treatment for MED or other disorders. Potentiation of mixed .alpha.,.beta.-blockers, like carvedilol, which is employed in treatment of hypertension, also is expected. Similarly, .alpha..sub.2 -adrenergic blockers, like yohimbine, can be potentiated.

SUMM Angiotensin converting enzyme (ACE) inhibitors block the conversion of angiotensin I into angiotensin II, which causes systemic vasoconstriction and the retention of sodium and water. **PDE5** inhibitors cause **vasodilation** in hypertensive animals, and stimulate the excretion of sodium and water in normotensive animals. Therefore, a **PDE5** inhibitor of formula (I) can be combined with an ACE inhibitor to achieve more powerful **vasodilatory** and natriuretic effects in, for example, treatment of congestive heart failure or hypertensive states.

CLM What is claimed is:
13. A method of **treating** stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, chronic obstructive pulmonary disease, malignant hypertension, pheochromacytoma, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic **ulcer**, a gut motility disorder, pospercutaneous transluminal coronary angioplasty, carotid angioplasty,

post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy, or irritable bowel syndrome, in a human or nonhuman animal body, said method comprising administering to said body a therapeutically effective amount of a combination of claim 1.

PI US 6043252 20000328

L40 ANSWER 16 OF 90 USPATFULL

SUMM In summary, the biochemical, physiological, and clinical effects of **PDE5** inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, **inflammatory**, and/or endocrine function is desirable. The compounds of formula (I), therefore, have utility in the treatment of a number of disorders, including stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, acute respiratory distress syndrome, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., postpercutaneous transluminal coronary or carotid angioplasty, or post-bypass surgery graft stenosis), peripheral vascular disease, vascular disorders, such as Raynaud's disease, thrombocythemia, **inflammatory** diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm labor, benign prostatic hypertrophy, male and female erectile dysfunction, and diseases characterized by disorders of gut motility (e.g., irritable bowel syndrome).

SUMM The present selective **PDE5** inhibitors in combination with **vasodilators**, including nitric oxide and nitric oxide donators and precursors, such as the organic nitrate **vasodilators** which act by releasing nitric oxide in vivo, are especially useful in treatment of angina, congestive heart failure, and malignant hypertension (e.g., pheochromocytoma). Related to the capacity of the present **PDE5** inhibitors to potentiate nitric oxide donors and precursors is their ability, in spontaneously hypertensive rats, to reverse the desensitization to these agents that occurs with chronic use.

SUMM Alph.alpha.-adrenergic blockers inhibit vasoconstriction in the corpus cavernosum. Because **PDE5** inhibitors enhance **vasodilation** of the same smooth muscle tissue, a **PDE5** inhibitor of formula (I) and an .alpha.-adrenergic blocker, like phentolamine or prazocin, or a centrally acting dopaminergic agent, like apomorphine, can be expected to potentiate one another in a treatment for MED or other disorders. Potentiation of mixed .alpha.,.beta.-blockers, like carvedilol, which is employed in treatment of hypertension, also is expected Similarly, .alpha..sub.2 -adrenergic blockers, like yohimbine, can be potentiated.

SUMM Angiotensin converting enzyme (ACE) inhibitors block the conversion of angiotensin I into angiotensin II, which causes systemic vasoconstriction and the retention of sodium and water. **PDE5** inhibitors cause **vasodilation** in hypertensive animals, and stimulate the excretion of sodium and water in normotensive animals. Therefore, a **PDE5** inhibitor of formula (I) can be combined with an ACE inhibitor to achieve more powerful **vasodilatory** and natriuretic effects in, for example, treatment of congestive heart failure or hypertensive states.

CLM What is claimed is:
12. A method of **treating** stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, malignant hypertension, pheochromocytoma, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic **ulcer**, a gut motility disorder, postpercutaneous transluminal coronary or carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign

prostatic hypertrophy, or irritable bowel syndrome, in a human or nonhuman animal body, said method comprising administering to said body a therapeutically effective amount of a combination of claim 1.

PI US 6143746 20001107

L84 ANSWER 32 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AB An animal model suitable for study of the origin and method of prevention of thromboembolic complications of arterial prostheses has been developed in the rabbit. In phase I of the experiments 42 New Zealand white rabbits underwent insertion of polytetrafluoroethylene (PTFE) aortic grafts, 10 mm in length and of 2 mm internal diameter (I.D.) (n=17) and 3 mm I.D.(n=25). The patency rate at 3 months was 24% and 82%, respectively. Unexpected ischemic hind limb **ulcers** occurred in nine (38%) of the long-term survivors. Arteriograms in these animals showed a typical embolic occlusion of a distal artery, suggesting that the **ulcers** were due to embolization of loose mural thrombus, which was present in 50% of the grafts when removed. In phase II experiments 54 rabbits were randomly allocated to receive aspirin (ASA) 10 mg/kg/day and **dipyridamole** (DPM) 10 mg/kg/day (n=25)or placebo (n=29). Both regimens began 3 days before insertion of PTFE aortic grafts (10 mm long and 3 mm I.D.). Serum thromboxane B2 concentrations in the control group averaged 300.4 .+-. 147.4 ng/ml and 43.2 .+-. 58.6 ng/ml in the ASA/DPM group (p<0.0005). With the use of autologous indium 111 oxine-labeled platelets, a graft platelet accumulation index (GPAI) was calculated as the graft:reference ratio of emissions. ASA/DPM significantly reduced the mean GPAI calculated from grafts and reference aorta removed 48 hours after graft insertion from 69.3 .+-. 4.0 on placebo (n=4) to 34.3 .+-. 2.9 (n=4) (p<0.001). At 3 months eight (33%) of the remaining 24 control animals had hind limb **ulcers** 31.0 .+-. 22.5 days post-operatively, whereas none occurred among the 19 animals **treated** with antiplatelet agents (p<0.01). This correlation of ASA/DPM reduction of platelet accumulation on PTFE grafts with prevention of thromboembolic complications suggests that patients receiving small-diameter PTFE grafts should be considered candidates for long-term antiplatelet therapy.

ACCESSION NUMBER: 87068115 EMBASE
DOCUMENT NUMBER: 1987068115
TITLE: Platelet antagonists eliminate thromboembolic complications of small-diameter polytetrafluoroethylene arterial prostheses.
AUTHOR: Nordestgaard A.G.; Buckels J.A.C.; Wilson S.E.
CORPORATE SOURCE: Department of Surgery, Harbor/UCLA Medical Center, Torrance, CA 90509, United States
SOURCE: Journal of Vascular Surgery, (1987) 5/1 (110-117).
CODEN: JVSUES
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
009 Surgery
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
030 Phar

L84 ANSWER 31 OF 38 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AB This article reviews the effects of pentoxifylline on red cells, white cells. platelets, and other blood elements and describes its synergism with calcium channel blockers and **dipyridamole**.
Treatment of necrobiotic granulomata, vasculitides, cryoglobulinemia, leg **ulcers**, diabetic complications, and potential new uses are discussed.

ACCESSION NUMBER: 88273025 EMBASE
DOCUMENT NUMBER: 1988273025
TITLE: Pentoxifylline therapy in dermatology. A review of localized hyperviscosity and its effects on the skin.
AUTHOR: Ely H.
CORPORATE SOURCE: Department of Dermatology, University of California, Davis, CA, United States
SOURCE: Dermatologic Clinics, (1988) 6/4 (585-608).
ISSN: 0733-8635 CODEN: DRMCDJ
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 013 Dermatology and Venereology
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

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      FILE 'USPATFULL' ENTERED AT 19:03:50 ON 03 OCT 2002
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L2           142 S DECUBITUS/AB OR (VENOUS ULCER? OR ATERIAL ULCERS)/AB
L3            72 S L1 AND L2
L4            72 FOCUS L3 1-
L5        184352 S TREAT?/CLM
L6            30 S L5 AND L3
L7            30 FOCUS L6 1-
L8             3 S L3 AND (PDE? OR MMP?)

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L# LIST L1-L8 HAS BEEN SAVED AS 'L09927344/L'

=> save l8
ENTER NAME OR (END):a09927344/a
ANSWER SET L8 HAS BEEN SAVED AS 'A09927344/A'

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L18 ANSWER 1 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
AN 2000408695 EMBASE
TI Adenosine- and adenine-nucleotide-mediated inhibition of normal and transformed keratinocyte proliferation is dependent upon dipyridamole-sensitive adenosine transport.
AU Brown J.R.; Cornell K.; Cook P.W.
CS Dr. P.W. Cook, Division of Molecular Medicine NRC 3, Oregon Health Sciences University, Portland, OR 97201, United States. cookp@ohsu.edu
SO Journal of Investigative Dermatology (2000) 115/5 (849-859).
Refs: 74
ISSN: 0022-202X CODEN: JIDEAE
CY United States
DT Journal; Article
FS 013 Dermatology and Venereology
029 Clinical Biochemistry
LA English
SL English
AB Extracellular adenosine and its related nucleotides have been referred to as retaliatory metabolites that can be released into the extracellular environment during inflammation, **wounding**, and other pathologic states. We have previously reported that these compounds reversibly inhibit the proliferation of normal keratinocyte cultures and we now demonstrate that these compounds also arrest the proliferation of transformed keratinocytes. Although our study shows that keratinocytes express mRNA corresponding to the A2B purinoreceptors and that adenosine or AMP **treatment** elevates intracellular cAMP in these cells, our study also demonstrates that **dipyridamole**-inhibitable transport of adenosine into the keratinocyte is central to the mechanism by which adenosine and adenine nucleotides arrest proliferation in these cells. In support of this mechanism, our results demonstrate that human keratinocytes express mRNA corresponding to the recently cloned **dipyridamole**-sensitive human equilibrative nucleoside transporter. Interestingly, coincubation with adenosine deaminase reverses the antiproliferative action of adenosine and exerts no effect on the antiproliferative activity of the adenine nucleotides, thus supporting a model in which adenine nucleotides are enzymatically converted to adenosine and transported into the keratinocyte in a tightly coupled and adenosine-deaminase-resistant manner. Analysis of adenosine- and adenosine-monophosphate-**treated** keratinocytes demonstrated that quiescence is induced within 12-24h, and fluorescence-activated cell sorter analysis suggests that **treatment** with these compounds may result in the inhibition of keratinocyte proliferation at both G1 and S phases of the cell cycle. In addition to their documented antiproliferative action on other cell types, adenosine, adenine nucleotides, and related analogs may also represent a potential new class of pharmacologic regulators of keratinocyte proliferation in vivo.
CT Medical Descriptors:
*keratinocyte
*cell proliferation
mitosis inhibition
purine metabolism
cell membrane transport
transport kinetics
human
normal human
controlled study
human cell
article
priority journal
Drug Descriptors:
*adenosine
*adenine nucleotide

*dipyridamole
messenger RNA: EC, endogenous compound
cyclic AMP: EC, endogenous compound
adenosine A2b receptor: EC, endogenous compound
RN (adenosine) 58-61-7; (dipyridamole) 58-32-2; (cyclic AMP) 60-92-4

L18 ANSWER 2 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 2
AN 2000378031 EMBASE
TI Suggested treatment protocol for improving patency of femoral-infrapopliteal cryopreserved saphenous vein allografts.
AU Buckley C.J.; Abernathy S.; Lee S.D.; Arko F.R.; Patterson D.E.; Manning L.G.; Harris L.M.
CS Dr. C.J. Buckley, FACS, Division of Vascular Surgery, Scott and White Clinic, 2401 S 31st Street, Temple, TX 76508, United States. slee@swmail.sw.org
SO Journal of Vascular Surgery, (2000) 32/4 (731-738).
Refs: 33
ISSN: 0741-5214 CODEN: JVSUES
CY United States
DT Journal; Article
FS 009 Surgery
036 Health Policy, Economics and Management
037 Drug Literature Index
LA English
SL English
AB Purpose: Cryopreserved saphenous vein allografts are used for femoral-infrapopliteal bypass graft purposes when adequate autogenous vein is unavailable. Anticoagulation, immunosuppression therapy, or both have been suggested means for improving allograft patency. Immunosuppression has significant cost and morbidity and has produced variable results. Our successful **treatment** of luminal surface hypercoagulability associated with certain endovascular procedures prompted the use of an anticoagulation protocol prospectively to improve graft patency and limb salvage for patients receiving femoral-infrapopliteal cryopreserved saphenous vein allografts. Methods: Between September 1995 and October 1999, 24 patients (15 men and nine women) were enrolled in a prospective clinical trial for salvage of 26 severely ischemic lower limbs with femoral-infrapopliteal cryopreserved saphenous vein allograft bypass grafts. All patients were **treated** with a protocol (aspirin, low-dose heparin, low molecular weight dextran 40, **dipyridamole**, and warfarin), and no immunosuppressive agents were used. The cryopreserved saphenous vein allografts were matched to patients by ABO and Rh compatibility. Indications for revascularization were ischemic rest pain (n = 8), nonhealing **ulcer** (n = 13), or focal gangrene (n = 5), and no usable autogenous vein was available. Follow-up ranged from 2 to 35 months (mean, 19 months). We studied the location and type of outflow anastomosis, specific outflow vessel, morbidity, death, secondary procedures (digital/transmetatarsal amputation), and complications related to the **treatment** protocol. Life table analyses of primary graft patency and limb salvage were compared with other current reported data. Results: Primary graft patency with Kaplan-Meier life table analysis was 96% at 6 months, 87% at 12 months, and 82% at 18 and 24 months. There were no reoperations for acute graft occlusion. One graft underwent late segmental aneurysmal degeneration and rupture. There were no procedure-related deaths or bleeding complications. During late follow-up, anticoagulation was discontinued in three patients (12%) because of gastrointestinal bleeding. Limb salvage was 88% at 6 months and 80% at 12, 18, and 24 months. Patients returned to ambulatory status that was limited only by their other comorbidities. Conclusion: Femoral-infrapopliteal bypass graft for limb salvage with a cryopreserved saphenous vein allograft can be an acceptable alternative when autogenous vein is not available. Our **treatment** protocol substantially improved allograft patency and limb salvage when compared with current published data.

*stomach ulcer: PC, prevention
*stomach ulcer: DT, drug therapy
animal model
hypothermia
immobilization stress
pylorus ligation
rat
stomach perfusion
animal experiment
nonhuman
male
female
intraperitoneal drug administration
subcutaneous drug administration
article
priority journal
Drug Descriptors:
alcohol
hydrochloric acid
sodium hydroxide
thiol group
*dipyridamole: PD, pharmacology
*dipyridamole: DT, drug therapy
cimetidine
histamine
indometacin

RN (alcohol) 64-17-5; (hydrochloric acid) 7647-01-0; (sodium hydroxide) 1310-73-2; (dipyridamole) 58-32-2; (cimetidine) 51481-61-9, 70059-30-2; (histamine) 51-45-6, 56-92-8, 93443-21-1; (indometacin) 53-86-1, 74252-25-8, 7681-54-1

CO Sigma (United States); Fluka (Switzerland); Smith kline and french (United Kingdom)

L18 ANSWER 6 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 6

AN 88047866 EMBASE

DN 1988047866

TI Antithrombotic treatment in livedo vasculitis.

AU Yamamoto M.; Danno K.; Shio H.; Imamura S.

CS Dermatology Section, Tenri Hospital, Tenri-City 632, Japan

SO Journal of the American Academy of Dermatology, (1988) 18/1 I (57-62). ISSN: 0190-9622 CODEN: JAADDB

CY United States

DT Journal

FS 013 Dermatology and Venereology
037 Drug Literature Index
025 Hematology

LA English

SL English

AB Two patients with livedo vasculitis were **treated** successfully with antiplatelet drugs including ticlopidine hydrochloride, **dipyridamole**, and low-dose aspirin. Increased platelet functions were restored 1 week after the beginning of the **treatment**, followed by dramatic improvement of painful leg **ulcers** within 1 month. Livedo status was unchanged. We claim that anitplatelet therapy should be the first choice of **treatment** in this disease.

CT Medical Descriptors:
*leg ulcer
*segmented hyalinizing vasculitis
*thrombocyte function
adult
histology
priority journal
case report
human

drugs affecting the platelet function.
AU Johnsson H.; Olsson P.
CS Dept. Blood Coagulat., Thorac. Clin., Karolinska Sjukh., Stockholm, Sweden
SO Haemostasis, (1976) 5/1 (27-37).
CODEN: HMTSB7
DT Journal
FS 037 Drug Literature Index
025 Hematology
030 Pharmacology
LA English
AB Acetylsalicylic acid and phenylbutazone increased the bleeding significantly from standardized **wounds** in dogs defibrinogenated with Defibrase. Administration of **dipyridamole** and Xylocain had no effect. The results were the same in dogs **treated** with warfarin sodium. The results demonstrate the value of using laboratory animals with an induced coagulopathy when establishing the effect on the haemostasis exerted by drugs known in vitro to interfere with platelet functions. Acetylsalicylic acid and **dipyridamole** did not alter the activity of the K vitamin dependent coagulation factors, factors V, VIII, platelet count or fibrinogen concentration.
CT Medical Descriptors:
*blood clotting disorder
*dog
*hemostasis
*thrombocyte
*thrombocyte count
theoretical study
Drug Descriptors:
*acetylsalicylic acid
*blood clotting factor 5
*blood clotting factor 8
*citrate sodium
*batroxobin
*dipyridamole
*fibrinogen
*lidocaine
*phenylbutazone
*thromboplastin
*warfarin
symplastin a
unclassified drug
RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (blood clotting factor 5) 9001-24-5, 9013-23-4; (blood clotting factor 8) 9001-27-8; (citrate sodium) 18996-35-5, 994-36-5; (batroxobin) 9039-61-6; (dipyridamole) 58-32-2; (fibrinogen) 9001-32-5; (lidocaine) 137-58-6, 24847-67-4, 56934-02-2, 73-78-9; (phenylbutazone) 129-18-0, 50-33-9, 8054-70-4; (thromboplastin) 9035-58-9; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2
CN Defibrase; Waran; Persantin; Butazolidin; Xylocain; Symplastin a; Thromboplastin
CO Astra (Switzerland); Pentapharm (Switzerland); Nyegaard; Warner lambert (United States); Boehringer (Germany); Ciba geigy (Switzerland); General diagnostics

L18 ANSWER 9 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 9
AN 76142219 EMBASE
DN 1976142219
TI The treatment of rejection: a trial of acetylsalicylic acid, dipyridamole, and heparin.
AU George C.R.P.; Slichter S.J.; Quadracci L.J.; et al.
CS Dept. Med., Univ. Washington, Seattle, Wash. 98195, United States
SO Transplantation, (1975) 20/3 (237-240).
CODEN: TRPLAU
DT Journal

FS 037 Drug Literature Index
026 Immunology, Serology and Transplantation
030 Pharmacology
025 Hematology
LA English
AB Serial studies of platelet and fibrinogen survival were performed in 26 nonimmunosuppressed dogs after allogenic renal transplant operations. **Treatment** with acetylsalicylic acid, **dipyridamole**, and heparin failed to improve the selective platelet destruction which occurred in untreated animals, and it did not improve postoperative longevity. There was a high incidence of postoperative **wound** and intrarenal hemorrhage after heparin **treatment**. These results are consistent with the hypothesis that platelet destruction is a consequence rather than the cause of acute graft rejection, and it is concluded that antithrombotic therapy is not of practical benefit in preventing acute rejection
CT Medical Descriptors:
*graft survival
*dog
*graft rejection
*graft versus host reaction
*hemostasis
*immunosuppressive treatment
*kidney graft
*kidney hemorrhage
*kidney transplantation
*thrombocyte
*thrombocyte lifespan
theoretical study
statistics
Drug Descriptors:
*acetylsalicylic acid
*dipyridamole
*fibrinogen
*heparin
*penicillin g
*streptomycin
RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (fibrinogen) 9001-32-5; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (penicillin g) 1406-05-9, 61-33-6; (streptomycin) 57-92-1

L18 ANSWER 10 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001209540 EMBASE
TI Clinical correlates and drug treatment of residents with stroke in long-term care.
AU Quilliam B.J.; Lapane K.L.
CS Dr. K.L. Lapane, Brown University, Box G-B222, Providence, RI 02912, United States. Kate_Lapane@brown.edu
SO Stroke, (2001) 32/6 (1385-1392).
Refs: 66
ISSN: 0039-2499 CODEN: SJCCA7
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
037 Drug Literature Index
LA English
SL English
AB Background and Purpose - Stroke incidence increases with age, and stroke survivors often require nursing home placement. Characteristics of these residents and factors associated with the secondary drug prevention of stroke in nursing homes have yet to be explored. Methods - We used a population-based data set of all nursing home residents in 5 states (1992 to 1995). We identified 53 829 (20.4%) with a diagnosis of stroke on the

Minimum Data Set assessment. We considered aspirin, **dipyridamole**, ticlopidine, or warfarin alone or in combination as secondary drug prevention. We used logistic regression modeling to identify independent predictors of drug **treatment**. Results - Sixty-seven percent of stroke survivors were not receiving drug therapy for stroke prevention. Among those **treated**, most received aspirin alone (16%) or warfarin alone (10%). Independent predictors of drug **treatment** included comorbid conditions (eg, hypertension, atrial fibrillation, depression, Alzheimer's disease, dementia, gastrointestinal bleeding, and peptic **ulcer** disease). Those over the age of 85 years were less likely to be **treated** than those 65 to 74 years of age (odds ratio [OR], 0.86; 95% confidence interval [CI], 0.82 to 0.91); black residents were less likely to be **treated** than whites (OR, 0.80; 95% CI, 0.75 to 0.85); and those with severe cognitive (OR, 0.63; 95% CI, 0.60 to 0.67) or physical impairment (OR, 0.69; 95% CI, 0.64 to 0.75) were also less likely to receive drug **treatment**. Conclusions - Stroke is highly prevalent in long-term care. Despite the increased risk of subsequent stroke in the elderly, many are not being **treated**. The choice to **treat** or not to **treat** may be influenced by age, comorbidity, race/ethnicity, and cognitive or physical functioning.

CT Medical Descriptors:
*stroke: DT, drug therapy
*stroke: PC, prevention
*long term care
nursing home
comorbidity
hypertension
heart atrium fibrillation
depression
Alzheimer disease
dementia
peptic ulcer
gastrointestinal hemorrhage
cognitive defect
ethnic difference
human
male
female
major clinical study
aged
article
priority journal
Drug Descriptors:
*acetylsalicylic acid: DT, drug therapy
*dipyridamole: DT, drug therapy
*ticlopidine: DT, drug therapy
*warfarin: DT, drug therapy

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (ticlopidine) 53885-35-1, 55142-85-3; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2

L18 ANSWER 11 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001176942 EMBASE
TI Livedoid vasculitis: A clinico-pathological study of 19 patients.
AU Jang K.-A.; Kim C.-H.; Kim S.-H.; Choi J.-H.; Sung K.-J.; Moon K.-C.; Koh J.-K.
CS Dr. K.-A. Jang, Department of Dermatology, Paik Hospital, Inje-University, Seoul, Korea, Republic of. jang722@netsgo.com
SO Korean Journal of Dermatology, (2001) 39/2 (147-154).
Refs: 43
ISSN: 0494-4739 CODEN: TPKCAW
CY Korea, Republic of
DT Journal; Article

FS 005 General Pathology and Pathological Anatomy
013 Dermatology and Venereology
037 Drug Literature Index
LA Korean
SL English; Korean
AB Background: Livedoid vasculitis is a distinctive dermatosis characterized by recurrent chronic **ulceration** and infiltrated purpuric papules on the lower limbs. Objective: The purpose of this study was aimed at evaluating the clinical and histopathological features of livedoid vasculitis. Methods:The hospital charts and histopathologic slides of patients with livedoid vasculitis diagnosed at Asan Medical Center from 1989 to 1999 were reviewed.Results: Twelve male and seven female patients were enrolled in this study(M : F=1.7: 1). The mean age at onset was 30.3 years in men and 25.3 years in women. The mean duration of illness was 3.3 years in male patients and 5.7 years in female patients. All the patients were presented with recurrent chronic **ulceration** and atrophic scarring. Twelve patients(63.2%) complained of severe pain and tenderness of the lesions and 5 patients(26.3%) complained of itching sensation. In three patients(15.8%), the lesions developed or aggravated in summer. Alcohol intake was aggravating factor in two patients(10.5%) and smoking was in one patient(5.3%). In five patients(26.3%), livedoid vasculitis develops in association with several diseases. Associated diseases were diabetes mellitus in 2 patients(10.5%), antiphospholipids antibody syndrome in 2 patients(10.5%), and protein S deficiency in 1 patient(5.3%). Histopathological examination revealed hyalinized blood vessels, partial to complete obstruction of dermal blood vessels with fibrinoid thrombi, endothelial swelling, and extravasation of RBCs in upper and mid-dermis. Panniculitis-like feature was common finding(73%). In six patients(31%), moderate to severe inflammatory reaction was observed in dermis. Five patients were **treated** with aspirin, **dipyridamole**, and pentoxifylline, and among them, only 1 patient(20%) were improved. All the **treatment** response including pentoxifylline alone, or pentoxifylline plus aspirin, **dipyridamole** , or corticosteroid was unsatisfactory. In cases of three patients whom were **treated** with low-dose danazol, all the patients(100%) showed marked improvement. One patient was **treated** with dapsone with improvement. Conclusion: Livedoid vasculitis is a distinct dermatosis with characteristic clinico-pathological features. Low-dose danazol or dapsone may be useful therapeutic options in this intractable disease.
CT Medical Descriptors:
*vasculitis: DT, drug therapy
*skin disease: DT, drug therapy
recurrent disease
histopathology
scar formation
clinical feature
pain: CO, complication
disease severity
pruritus: CO, complication
alcohol consumption
disease association
non insulin dependent diabetes mellitus
antiphospholipid syndrome
protein S deficiency
inflammation
treatment outcome
treatment failure
human
male
female
clinical article
article
Drug Descriptors:
acetylsalicylic acid: CB, drug combination

acetylsalicylic acid: DT, drug therapy
dipyridamole: CB, drug combination
dipyridamole: DT, drug therapy
pentoxifylline: CB, drug combination
pentoxifylline: DT, drug therapy
corticosteroid: CB, drug combination
corticosteroid: DT, drug therapy
danazol: DO, drug dose
danazol: DT, drug therapy
dapsone: DT, drug therapy

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (pentoxifylline) 6493-05-6; (danazol) 17230-88-5; (dapsone) 80-08-0

L18 ANSWER 12 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 2000096837 EMBASE

TI Negative impact of cardiac evaluation before vascular surgery.

AU Krupski W.C.; Nehler M.R.; Whitehill T.A.; Lawson R.C.; Strecker P.K.; Hiatt W.R.

CS W.C. Krupski, Department of Surgery, Campus Box C-312, Univ. of Colorado Hlth. Sci. Center, 4200 East Ninth Avenue, Denver, CO 80262, United States

SO Vascular Medicine, (2000) 5/1 (3-9).
Refs: 49
ISSN: 1358-863X CODEN: VAMLFP

CY United Kingdom

DT Journal; Article

FS 009 Surgery
018 Cardiovascular Diseases and Cardiovascular Surgery

LA English

SL English

AB The optimal preoperative evaluation of cardiac risk in patients with peripheral vascular disease is controversial. In developing a paradigm for preoperative cardiac workup, potential adverse effects of evaluation and cardiac intervention must be considered. This study analyzed the deleterious outcomes of extensive, comprehensive cardiac evaluation and intervention before planned vascular surgery in patients **treated** at the Denver Department of Veterans Affairs Medical Center. Over a 12-month period between 1994 and 1995, 161 patients were scheduled to undergo major vascular operations; 153 patients came to operation. The decision to pursue a cardiac evaluation was variously made by a combination of surgeons, cardiologists, and anesthesiologists. No defined protocol was followed. Cardiac history, chest X-rays and ECGs were obtained for all patients. Extended cardiac evaluation included these studies plus special tests, including echocardiography (echo), radionuclide ventriculography (RNVG), **dipyridamole** thallium scintigraphy (DTS), and cardiac catheterization (CC). Extended cardiac evaluations were undertaken in 42 patients. Complications related to percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) were also recorded. Cardiac mortality and morbidity after vascular interventions were itemized in all 153 patients. Forty-two male patients, aged 68 .+-. 9 years, underwent extended cardiac evaluations before planned vascular operations. The median elapsed time for cardiac workup was 14 days (mean 30 .+-. 59 days). The median and mean times from cardiac workup to vascular surgery were 25 days and 76 .+-. 142 days, respectively. Eighteen (43%) patients had echo or RNVG; 22 (52%) patients had DTS; 27 (64%) had CC; 9 (21%) had PTCA; 7 (17%) had CABG. Sixteen (38%) patients had untoward events related to cardiac evaluation. Eight patients (19%: one with cerebrovascular disease, and seven with aortic aneurysms) refused vascular surgery after extended cardiac workup. Complications attributable to CC, PTCA, and CABG included prosthetic graft infection, pseudoaneurysms (two), sternal **wound** infections (two), renal failure and brain anoxia. Two patients with severe limb ischemia who were candidates for revascularization ultimately required amputations because of delay due to cardiac evaluations. Extensive cardiac

evaluation prior to vascular operations can result in morbidity, delays, and refusal to undergo vascular surgery. The underlying indication for vascular operations and the local iatrogenic cardiac complication rates must be considered before ordering special studies.

CT Medical Descriptors:
*vascular surgery
*peripheral vascular disease: SU, surgery
*coronary artery disease: DI, diagnosis
*coronary artery disease: SU, surgery
preoperative evaluation
treatment outcome
thorax radiography
electrocardiogram
echocardiography
radioisotope ventriculography
heart scintiscanning
heart catheterization
transluminal coronary angioplasty
coronary artery bypass graft
graft infection: CO, complication
false aneurysm: CO, complication
wound infection: CO, complication
kidney failure: CO, complication
brain hypoxia: CO, complication
limb ischemia: SU, surgery
limb amputation
angina pectoris
congestive heart failure
hypertension
human
male
clinical article
controlled study
aged
adult
article
priority journal
Drug Descriptors:
thallium
dipyridamole

RN (thallium) 22537-56-0, 7440-28-0; (dipyridamole) 58-32-2

L18 ANSWER 13 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 96126259 EMBASE
DN 1996126259
TI [Livedo vasculitis with summer ulceration. Therapy with pentoxifylline and dipyridamole].
VASCULITIS LIVEDOIDE CON ULCERAS DE VERANO. TRATAMIENTO CON PENTOXIFILLINA Y DIPIRADAMOL.
AU Just M.; Ribera M.; Bielsa I.; Paradelo C.; Ferrandiz C.
CS Servicio de Dermatologia, Hosp. Univ. Germans Trias i Pujol, Ctra. del Caryet, s/n,08916 Badalona, Spain
SO Actas Dermo-Sifiliograficas, (1996) 87/4 (199-203).
ISSN: 0001-7310 CODEN: ADSIAZ
CY Spain
DT Journal; Article
FS 013 Dermatology and Venereology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA Spanish
SL Spanish; English
AB Livedo vasculitis with summer **ulceration** appears as painful **ulcerations** on the lower legs. Histologically, it shows thrombotic

occlusion of small vessels in the middle dermis without vasculitis. Although this condition has been reported in association with several systemic diseases, most cases seem to be idiopathic. Three cases which dramatically improve by combination **treatment** with pentoxifylline and **dipyridamole** are reported. Pentoxifylline has multiple mechanisms of action, most of which may contribute to its successful use in the **treatment** of idiopathic livedo vasculitis.

CT Medical Descriptors:
*leg ulcer: DT, drug therapy
adult
article
case report
drug efficacy
female
histology
human
male
oral drug administration
segmented hyalinizing vasculitis: DT, drug therapy
thrombosis
Drug Descriptors:
*dipyridamole: DT, drug therapy
*dipyridamole: CB, drug combination
*pentoxifylline: DT, drug therapy
*pentoxifylline: CB, drug combination

RN (dipyridamole) 58-32-2; (pentoxifylline) 6493-05-6

L18 ANSWER 14 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 94197409 EMBASE
DN 1994197409
TI Three cases of livedo vasculitis cleared by combined therapy of acetylsalicylic acid, dipyridamole and nifedipine.
AU Yoon T.Y.; Chang S.H.
CS Department of Dermatology, College of Medicine, Chungbuk National University,Cheongju, Korea, Republic of
SO Korean Journal of Dermatology, (1994) 32/2 (294-299).
ISSN: 0494-4739 CODEN: TPKCAW
CY Korea, Republic of
DT Journal; Article
FS 013 Dermatology and Venereology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA Japanese
SL English
AB Livedo vasculitis clinically shows purpuric papules and recurrent **ulcers** in the lower extremities, mainly on the ankles, leaving characteristic scars called atrophie blanche after the healing of the **ulcers**. Its characteristic histopathologic features and clinical evolution indicate that the common pathologic event is occlusion of vessels in the middle and deep dermis. In Korean literature, seven cases of this disease have been reported but the response of the **treatment** was not satisfactory. We report three cases of livedo vasculitis cleared by combined therapy of acetylsalicylic acid, **dipyridamole** and nifedipine, which has not been reported in Korean literature.

CT Medical Descriptors:
*skin ulcer: DT, drug therapy
*vasculitis: DT, drug therapy
article
case report
human
recurrent peptic ulcer
ulcer healing

Drug Descriptors:
*acetylsalicylic acid: DT, drug therapy
*acetylsalicylic acid: CB, drug combination
*dipyridamole: DT, drug therapy
*dipyridamole: CB, drug combination
*nifedipine: DT, drug therapy
*nifedipine: CB, drug combination
RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (nifedipine) 21829-25-4

L18 ANSWER 15 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 93043858 EMBASE
DN 1993043858
TI Ulcerating necrobiosis lipoidica effectively treated with pentoxifylline.
AU Noz K.C.; Korstanje M.J.; Vermeer B.J.
CS Department of Dermatology, Academic Hospital, Rijnsburgerweg 10,2333 AA Leiden, Netherlands
SO Clinical and Experimental Dermatology, (1993) 18/1 (78-79).
ISSN: 0307-6938 CODEN: CEDEDE
CY United Kingdom
DT Journal; Article
FS 013 Dermatology and Venereology
037 Drug Literature Index
LA English
SL English
AB A 30-year-old man had suffered from persistent **ulceration** within an area of necrobiosis lipoidica diabeticorum for 13 months. The **ulcerating** necrobiosis lipoidica was resistant to topical therapy and oral therapy with acetylsalicylic acid. However, the **ulcers** healed completely within 8 weeks of administration of 400 mg pentoxifylline twice daily. Necrobiosis lipoidica has a unique diagnostic appearance. The clinical features, histopathology, pathogenesis and **treatment** are discussed extensively by Lowitt et al. The **treatment** of **ulcerating** necrobiosis lipoidica is difficult. Attempts have been made, with varying results, to **treat** necrobiosis lipoidica with topical corticosteroids, fibrinolytics and antiplatelet agents, e.g. acetylsalicyclic acid and **dipyridamole**, either alone or in combination. As pentoxifylline is effective in healing venous **ulcers** of the leg we decided to try this drug for the **treatment** of **ulcerating** necrobiosis lipoidica.
CT Medical Descriptors:
*insulin dependent diabetes mellitus
*skin ulcer: DT, drug therapy
*skin ulcer: CO, complication
adult
article
case report
human
male
oral drug administration
priority journal
topical drug administration
Drug Descriptors:
*acetylsalicylic acid: DT, drug therapy
*pentoxifylline: DT, drug therapy
RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (pentoxifylline) 6493-05-6

L18 ANSWER 16 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 91157199 EMBASE
DN 1991157199
TI Heat conductivity and skin temperature at the treatment of ischemic heart disease with curantyl and isoptin.
AU Kollar J.; Uhrik J.; Hejj F.

CS Institute of Experimental Medicine, University P.J. Safarik, Kosice, Czechoslovakia
SO International Angiology, (1991) 10/1 (34-37).
ISSN: 0392-9590 CODEN: INANEK
CY Italy
DT Journal; Article
FS 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English
AB Forty-one patients with ischemic heart disease (IHD) of the age 60 .+-. 12.3 years were hospitalized and **treated** two weeks with **Curantyl** (**Dipyridamole**) which was applied per os in a dose of 75 mg 3 times, and after another two weeks 34 of them were applied Isoptin (Verapamil) in a dose of 40 mg 3 times daily. The head conductivity (J.cntdot.m-1, sec-1.cntdot..degree.C.gtoreq.10-2, HC) and skin temperature (.degree.C, ST) were examined at the isothermic level 2 cm above the inner ankle by the apparatus Fluvograph 2 of Hartmann and Braun A.G. (BRD). The HC after Isoptin application above the left and right ankle was in 34 patients increased significantly ($p < 0.001$). In patients with IHD after **Curantyl** application the HC and ST was significantly decreased above the left and right ankle in 9 (21.9%) and in 12 (30.3%), respectively. **Curantyl** could deteriorate HC and so worsen legs **ulceration** healing and to point up ischemia in patients with associated chronic postphlebitis syndrome with **ulcera** crurium.
CT Medical Descriptors:
*heart muscle ischemia: DT, drug therapy
*skin temperature
*thermal conductivity
adult
aged
apparatus
article
clinical article
drug effect
human
leg blood flow
oral drug administration
Drug Descriptors:
*dipyridamole: DT, drug therapy
*verapamil: DT, drug therapy
RN (dipyridamole) 58-32-2; (verapamil) 152-11-4, 52-53-9
CN Curantyl; Isoptin

L18 ANSWER 17 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 90271981 EMBASE
DN 1990271981
TI Atherothrombotic microembolism of the lower extremities (the blue toe syndrome) from atherosclerotic non-aneurysmal aortic plaques.
AU Benvegna S.; Cassina I.; Giuntini G.; Rusignuolo F.; Talarico F.; Florena M.
CS Dipartimento di Discipline Chirurgiche ed Anatomiche, Cattedra di Patologia Chirurgica ''R'', Universita degli Studi di Palermo, Palermo, Italy
SO Journal of Cardiovascular Surgery, (1990) 31/1 (87-91).
ISSN: 0021-9509 CODEN: JCVSA2
CY Italy
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English

AB Six patients with no hemodynamically significant atherosclerotic lesions of the lower limb arteries but with ischemic changes of the feet or toes were studied and diagnosed as having atherothrombotic microembolism. All patients were non claudicators and had peripheral Doppler examinations on admission. Five patients experienced more than one separate episode of microembolization involving both extremities. None presented with a history of heart disease or diabetes. Biplanar arteriograms revealed in every case atherosclerotic degeneration of the aorta without any obstructing lesions and anatomical arterial continuity between the aorta and the site of distal embolization. Three patients who refused operation, were **treated** conservatively, with a combination of **dipyridamole** plus aspirin. Three other patients had surgical repair of their atheromatous infrarenal aorta: in two cases thromboendarterectomy was performed, and in the other a Dacron bifurcated graft interposition. No amputations resulted in the patients **treated** medically, but one of the surgical group lost one toe. This study confirms that atherothrombotic microembolism from an **ulcerated** atherosclerotic aorta is a potential threat to the extremities and indicates that the optimal therapy for this syndrome has yet to be found.

CT Medical Descriptors:
*atherosclerotic plaque: TH, therapy
*atherosclerotic plaque: DT, drug therapy
*leg artery
*microembolism: TH, therapy
*microembolism: DT, drug therapy
*thrombosis: TH, therapy
*thrombosis: DT, drug therapy
adult
aged
clinical article
human
male
female
article
Drug Descriptors:
*acetylsalicylic acid: DT, drug therapy
*dipyridamole: DT, drug therapy

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2

L18 ANSWER 18 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 88273025 EMBASE
DN 1988273025
TI Pentoxifylline therapy in dermatology. A review of localized hyperviscosity and its effects on the skin.
AU Ely H.
CS Department of Dermatology, University of California, Davis, CA, United States
SO Dermatologic Clinics, (1988) 6/4 (585-608).
ISSN: 0733-8635 CODEN: DRMCDJ
CY United States
DT Journal
FS 013 Dermatology and Venereology
025 Hematology
037 Drug Literature Index
LA English
SL English
AB This article reviews the effects of pentoxifylline on red cells, white cells, platelets, and other blood elements and describes its synergism with calcium channel blockers and **dipyridamole**. **Treatment** of necrobiotic granulomata, vasculitides, cryoglobulinemia, leg **ulcers**, diabetic complications, and potential new uses are discussed.

CT Medical Descriptors:
*blood viscosity
*diabetes mellitus: DT, drug therapy
*granuloma annulare: DT, drug therapy
*skin blood vessel
erythrocyte
leg ulcer
necrobiotic disorder
review
human
male
female
oral drug administration
Drug Descriptors:
fibrinogen
*acetylsalicylic acid: DT, drug therapy
*acetylsalicylic acid: IT, drug interaction
*calcium channel blocking agent: DT, drug therapy
*calcium channel blocking agent: IT, drug interaction
*dipyridamole: DT, drug therapy
*dipyridamole: IT, drug interaction
*pentoxifylline: PD, pharmacology
*pentoxifylline: DT, drug therapy
*pentoxifylline: IT, drug interaction
*warfarin: DT, drug therapy
*warfarin: IT, drug interaction
RN (fibrinogen) 9001-32-5; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (pentoxifylline) 6493-05-6; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2
CN (1) Trental
CO (1) Hoechst

L18 ANSWER 19 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 87068115 EMBASE
DN 1987068115
TI Platelet antagonists eliminate thromboembolic complications of small-diameter polytetrafluoroethylene arterial prostheses.
AU Nordestgaard A.G.; Buckels J.A.C.; Wilson S.E.
CS Department of Surgery, Harbor/UCLA Medical Center, Torrance, CA 90509, United States
SO Journal of Vascular Surgery, (1987) 5/1 (110-117).
CODEN: JVSUES
CY United States
DT Journal
FS 037 Drug Literature Index
009 Surgery
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
030 Pharmacology
014 Radiology
LA English
AB An animal model suitable for study of the origin and method of prevention of thromboembolic complications of arterial prostheses has been developed in the rabbit. In phase I of the experiments 42 New Zealand white rabbits underwent insertion of polytetrafluoroethylene (PTFE) aortic grafts, 10 mm in length and of 2 mm internal diameter (I.D.) (n=17) and 3 mm I.D.(n=25). The patency rate at 3 months was 24% and 82%, respectively. Unexpected ischemic hind limb **ulcers** occurred in nine (38%) of the long-term survivors. Arteriograms in these animals showed a typical embolic occlusion of a distal artery, suggesting that the **ulcers** were due to embolization of loose mural thrombus, which was present in 50% of the grafts when removed. In phase II experiments 54 rabbits were randomly allocated to receive aspirin (ASA) 10 mg/kg/day and

dipyridamole (DPM) 10 mg/kg/day (n=25)or placebo (n=29). Both regimens began 3 days before insertion of PTFE aortic grafts (10 mm long and 3 mm I.D.). Serum thromboxane B2 concentrations in the control group averaged 300.4 .+-. 147.4 ng/ml and 43.2 .+-. 58.6 ng/ml in the ASA/DPM group (p<0.0005). With the use of autologous indium 111 oxine-labeled platelets, a graft platelet accumulation index (GPAI) was calculated as the graft:reference ratio of emissions. ASA/DPM significantly reduced the mean GPAI calculated from grafts and reference aorta removed 48 hours after graft insertion from 69.3 .+-. 4.0 on placebo (n=4) to 34.3 .+-. 2.9 (n=4) (p<0.001). At 3 months eight (33%) of the remaining 24 control animals had hind limb **ulcers** 31.0 .+-. 22.5 days post-operatively, whereas none occurred among the 19 animals **treated** with antiplatelet agents (p<0.01). This correlation of ASA/DPM reduction of platelet accumulation on PTFE grafts with prevention of thromboembolic complications suggests that patients receiving small-diameter PTFE grafts should be considered candidates for long-term antiplatelet therapy.

CT Medical Descriptors:
*aorta
*artery prosthesis
*drug efficacy
*rabbit
*thromboembolism
angiography
priority journal
great blood vessel
oral drug administration
nonhuman
blood and hemopoietic system
animal experiment
cardiovascular system
peripheral vascular system
diagnosis
Drug Descriptors:
*antithrombocytic agent
*politef
*acetylsalicylic acid
*dipyridamole
8 quinolinol indium in 111
radioisotope

RN (politef) 9002-84-0, 9039-02-5; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (8 quinolinol indium in 111) 65389-08-4

CN Aspirin; Persantin

CO Plough; Boehringer ingelheim; Impra (United States)

L18 ANSWER 20 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 85059272 EMBASE

DN 1985059272

TI Perioperative antiplatelet therapy for aortocoronary artery bypass surgery.

AU Chesebro J.H.; Fuster V.

CS Mayo Clinic and Mayo Foundation, Rochester, MN 55905, United States

SO Modern Concepts of Cardiovascular Disease, (1984) 53/12 (65-70). CODEN: MCCDAV

CY United States

DT Journal

FS 037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery

LA English

AB The **dipyridamole** and aspirin therapy outlined in the table is standard at the Mayo Clinic and Mount Sinai Hospitals for patients undergoing aortocoronary vein bypass operations. For patients who are allergic to or intolerant of aspirin or who have had previous

gastrointestinal bleeding or gastric **ulcer**, there are two empiric alternatives: continue **dipyridamole**, 100 mg four times daily, without aspirin after operation, or use sulfinpyrazone, 200 mg four times daily, beginning 1 or 2 days before operation and continuing on the day of and after operation (one trial showing favorable benefit has been discussed). Platelt inhibitor therapy should be continued for at least one year and perhaps indefinitely, as suggested by the decreased lipid incorporation into vein grafts after administration of **dipyridamole** and aspirin in nonhuman primates. The ultimate results of our ongoing trial in the prevention of angiographic progression of coronary artery disease over 5 years in patients **treated** with **dipyridamole** and aspirin but without aortocoronary bypass surgery should also be helpful in determining whether therapy should be continued indefinitely.

CT Medical Descriptors:
*cancer chemotherapy
*coronary artery bypass graft
*heart infarction
*drug therapy
graft patency
therapy
heart
human
peripheral vascular system
blood and hemopoietic system
prevention
clinical article
Drug Descriptors:
*acetylsalicylic acid
*antithrombocytic agent
*dipyridamole
*placebo
*sulfinpyrazone

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (sulfinpyrazone) 57-96-5

CN Aspirin

L18 ANSWER 21 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 84042576 EMBASE

DN 1984042576

TI [Controlled trial of aspirin and dipyridamole in the secondary prevention of atherothrombotic cerebral ischemic accidents].
ESSAI COOPERATIF CONTROLE DE PREVENTION SECONDAIRE DES ACCIDENTS ISCHEMIQUES CEREBRAUX LIES A L'ATHEROSCLEROSE PAR L'ASPIRINE ET LE DIPYRIDAMOLE.

AU Bousser M.G.; Eschwege E.; Haguenau M.; et al.

CS Clinique des Maladies du Systeme Nerveux, Hopital de la Salpetriere, F 75013 Paris, France

SO Presse Medicale, (1983) 12/48 (3049-3057).
CODEN: PRMEEM

CY France

DT Journal

FS 037 Drug Literature Index
008 Neurology and Neurosurgery
020 Gerontology and Geriatrics
030 Pharmacology
025 Hematology

LA French

SL English

AB Six hundred and four patients with atherothrombotic cerebral ischemic events (transient: 16% or completed : 84%), either carotid or vertebral-basilar, entered into a double blind randomized clinical trial (AICLA) to determine whether aspirin (A) (1 g/day) or aspirin (1 g) + **dipyridamole** (225 mg) (AD) would produce a significant reduction

in the subsequent (3 years) occurrence of fatal and non fatal cerebral infarction. Randomization produced remarkably comparable **treatment** groups and this good comparability was maintained throughout the study. Adherence to the protocol and drug compliance were excellent. Side effects, particularly peptic **ulcers** and bleeding of various origins, were significantly ($p < 0.03$) more frequent in the two **treatment** groups containing aspirin. At the end of the study (3 years), the number of fatal and non fatal cerebral infarctions was 31 in the P group (placebo), 17 in the A group and 18 in the AD group. Taking into account the duration of follow up for each patient, these figures correspond to cumulative rates of 18% in the P group and 10.5% in the 2 others. Analysis with the Mantel method showed: a difference at the 6% level between the 3 groups and between P and AD; a difference at the 5% level between P and A; no difference between A and AD; a difference at the 2% level between the P group and the two **treated** groups taken together (A + AD). Among other diseases occurring during the trial, the only significant difference concerned myocardial infarction, less frequent in the 2 **treated** groups ($p < 0.05$). Subgroup analysis failed to show a significant sex difference in the efficacy of aspirin. It is concluded that, in patients such as those defined in the protocol, aspirin (1 g) has a significant beneficial effect in the secondary prevention of atherothrombotic cerebral infarction.

CT Medical Descriptors:
*brain infarction
*drug therapy
*stroke
*thrombocyte aggregation
*transient ischemic attack
controlled study
secondary prevention
central nervous system
therapy
oral drug administration
aged
clinical article
human
peripheral vascular system
blood and hemopoietic system
Drug Descriptors:
*acetylsalicylic acid
*dipyridamole
*placebo

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2

CN Aspirin

L18 ANSWER 22 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 83161155 EMBASE

DN 1983161155

TI Failure of topical prostaglandin inhibitors to improve wound healing following deep partial-thickness burns.

AU Fang C.; Alexander J.W.; MacMillan B.G.; Austin L.S.

CS Shriners Burns Inst., Cincinnati, OH 45219, United States

SO Journal of Trauma, (1983) 23/4 (300-304).
CODEN: JOTRA5

CY United States

DT Journal

FS 037 Drug Literature Index
009 Surgery
013 Dermatology and Venereology

LA English

AB The present study was designed to determine the efficacy of topical inhibitors of prostaglandins on **wound** healing. Two uniform deep partial-thickness burns were inflicted on mirror-image areas of guinea pig

backs by an aluminium template heated to 75.degree.C and applied for 10 seconds. Indomethacin was tested extensively in a wide range of concentrations in groups of six or more animals each. The healing rates measured at 21 days postburn showed that topical indomethacin at each concentration tested was not effective for improving **wound** healing. In fact, the **treated** sites were consistently worse than the control sites. Moreover, the drug adversely affected the healing process proportional to the concentration and was associated with death, which was related to perforations of the GI tract. Also, the India ink filling in the dermal microcirculation was no better in the experimental **wounds** than in the controls. The evaluations for hair growth were definitely in favor of the controls. The other tested inhibitors, ibuprofen, flurbiprofen, tolmetin, zomepirac, piroxicam, and **dipyridamole**, also failed to show any benefit.

CT Medical Descriptors:
*burn
*dose response
*drug comparison
*drug efficacy
*guinea pig
*wound healing
drug response
topical drug administration
controlled study
animal experiment
therapy
nonhuman
Drug Descriptors:
*dipyridamole
*flurbiprofen
*ibuprofen
*indometacin
*iodophor
*macrogol
*piroxicam
*polymacon
*prostaglandin inhibitor
*tolmetin

RN (dipyridamole) 58-32-2; (flurbiprofen) 5104-49-4; (ibuprofen) 15687-27-1; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (iodophor) 11096-42-7, 8037-86-3, 8038-05-9, 8050-84-8; (macrogol) 25322-68-3; (piroxicam) 36322-90-4; (polymacon) 25053-81-0, 25249-16-5, 98932-78-6; (tolmetin) 26171-23-3, 35711-34-3

CN Dermevan; Hydron

CO Abbott (United States); Parke davis (United States)

L18 ANSWER 23 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 83068840 EMBASE

DN 1983068840

TI 'AICLA' controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia.

AU Bousser M.G.; Eschwege E.; Haguenau M.; et al.

CS Clin. Mal. Syst. Nerv., Hop. Salpetriere, 75013 Paris, France

SO Stroke, (1983) 14/1 (5-14).
CODEN: SJCCA7

CY United States

DT Journal

FS 038 Adverse Reactions Titles
037 Drug Literature Index
008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
020 Gerontology and Geriatrics
025 Hematology

LA English

AB 604 Patients with atherothrombotic cerebral ischemic events (transient, 16%: or completed, 84%) referable either to the carotid or to the vertebral-basilar circulation were entered into a double blind randomized clinical trial (AICLA) to determine whether aspirin (A) (1 g/day) or aspirin (1 g/day) + **Dipyridamole** (225 mg/day) (AD) would produce a significant reduction in the subsequent (3 years) occurrence of fatal and nonfatal cerebral infarction. Randomization produced remarkably comparable **treatment** groups and this good comparability was maintained throughout the study. Adherence to the protocol and drug compliance were excellent. Side effects, particularly symptoms of peptic **ulcer** and hemorrhagic events were significantly ($p < 0.03$) more frequent in the two **treatment** groups containing aspirin. With the exception of patients who withdrew from this study, each patient was followed for 3 years. At the end of the study, the number of fatal and nonfatal cerebral infarctions was 31 in the placebo (P) group, 17 in the A group and 18 in the AD group. Taking into account the duration of follow-up for each patient, these figures correspond to cumulative rates of 18% in the P group and 10.5% in each of the 2 active **treatment** groups. Analysis with the Mantel Method showed: 1) - A difference at the 6% level between the 3 groups and between P and AD; 2) - A difference at the 5% level between P and A; 3) - No difference between A and AD; 4) - A difference at the 2% level between the P group and the two **treated** groups taken together (A + AD). Among other diseases occurring during the trial, the only significant difference concerned myocardial infarction, which was less frequent in the 2 **treated** groups ($P < 0.05$). Subgroup analysis failed to show a significant sex difference in the efficacy of aspirin. It is concluded that, in patients comparable to those defined in the protocol, Aspirin (1 g) has a significantly beneficial effect in the secondary prevention of atherothrombotic cerebral infarction.

CT Medical Descriptors:
*adverse drug reaction
*brain ischemia
*drug comparison
*gastrointestinal hemorrhage
*gastrointestinal symptom
*gastrointestinal toxicity
*peptic ulcer
*drug therapy
controlled study
prevention
central nervous system
digestive system
therapy
intoxication
oral drug administration
human
peripheral vascular system
major clinical study
Drug Descriptors:
*acetylsalicylic acid
*dipyridamole

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2

L18 ANSWER 24 OF 30 EMBASE
AN 81029421 EMBASE
DN 1981029421
TI Trial of dipyridamole-aspirin in recurring venous thrombosis.
AU Steele P.
CS Div. Cardiol., Dept. Med., Denver VA Med. Cent., Denver, Colo., United States
SO Lancet, (1980) 2/8208-8209 (1328-1329).
CODEN: LANCAO

CY United Kingdom
DT Journal
FS 037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
006 Internal Medicine
LA English
AB Thirty-eight patients (26 men) with recurring venous thromboembolism (RVTE) were enrolled in a prospective double-blind, placebo-controlled trial of **dipyridamole** (DPY), 100 mg a day, and aspirin (ASA), 1200 mg a day. Platelet survival (51Cr labelling of autologous platelets) was measured every 6 months for 18 months. Nineteen patients were randomized to **treatment** with DPY and ASA, and 1 had new venous thrombosis (after 15 months of **treatment**); 19 received placebo and 7 had new venous thrombosis (4-16 months later) (AHp2 = 5.70; $p<0.05$). DPY-ASA increased platelet survival whereas placebo **treatment** did not. The results suggest that in patients with RVTE and abnormal platelet survival time DPY in combination with ASA decreases the frequency of new venous thrombosis. Peptic **ulcers** developed in 2 patients **treated** with DPY-ASA.
CT Medical Descriptors:
*thrombocyte
*vein thrombosis
double blind procedure
peptic ulcer
peripheral vascular system
blood and hemopoietic system
major clinical study
therapy
controlled study
Drug Descriptors:
*acetylsalicylic acid
*dipyridamole
*placebo
*warfarin
RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2
CN Aspirin

L18 ANSWER 25 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 78194967 EMBASE
DN 1978194967
TI Antiplatelet treatment in septic shock with severe bleeding and thrombocytopenia.
AU Farina M.L.; Langer M.; Donati M.B.; Gaetano G.
CS Intens. Care Unit E. Vecla, Osp. Policlin., Milan, Italy
SO Thrombosis and Haemostasis, (1977) 38/2 (581-583).
CODEN: THAAT7
CY Germany
DT Journal
FS 037 Drug Literature Index
025 Hematology
009 Surgery
024 Anesthesiology
LA English
AB The authors have seen a patient with septic shock candidosis of the biliary ducts, severe hemorrhagic syndrome and marked thrombocytopenia, who was successfully **treated** with antiplatelet drugs, associated with replacement therapy and an antifibrinolytic agent. The patient was a 42-yr-old woman who had undergone cholecystectomy two years previously and had since suffered repeated episodes of abdominal pain with hyperpyrexia and jaundice. During one of the episodes, the patient was admitted to the surgical department. A few hours later, shock and anuria occurred; the

next day, despite massive fluid replacement, she was still in severe shock. At laparotomy, a stone occluding the choledochus was removed and Kehr drainage placed; neither hepato-splenomegaly nor other alterations of the abdominal organs was observed; profuse bleeding occurred during surgery. The patient was bleeding profusely from the surgical **wound**, the peritoneal drainage, the gastric cannula and the site of catheterization of the subclavian vein. Laboratory data obtained shortly thereafter showed severe thrombocytopenia but no gross laboratory abnormalities of the clotting and fibrinolytic systems. These data suggested there might be in vivo platelet consumption; **treatment** with **dipyridamole**, 25 mg every 6 hours, and lysine acetylsalicylate-L-ASA-, 450 mg every 12 hours i.v. was therefore associated with replacement therapy (red blood cells, fresh frozen plasma and platelet concentrates). Within 10 hours the shock subsided and diuresis started. On the second postoperative day, due to persistent severe thrombocytopenia and hemorrhagic syndrome, without signs of activated coagulation, **treatment** with E-aminocaproic acid-E-ACA-, 4 g every six hours i.v., was also instituted. From the third postoperative day, hemorrhage progressively decreased. Platelet transfusions were no longer administered after the fifth day, when the platelet count began to rise. **Treatment** with E-aminocaproic acid was stopped on the sixth day. Ten days after laparotomy, the patient was transferred to the wards; her general condition had markedly improved, no further bleeding had been reported and the platelet count had gradually reached the normal range. Oral antiaggregating **treatment** with **dipyridamole** alone, 420 mg per day, was prescribed.(Szirmai - Stuttgart)

CT Medical Descriptors:
*bleeding
*drug therapy
*septic shock
*thrombocytopenia
therapy
Drug Descriptors:
*acetoacetic acid
*aminocaproic acid
*dipyridamole
*lysine acetylsalicylate

RN (acetoacetic acid) 541-50-4, 623-58-5; (aminocaproic acid) 1319-82-0, 60-32-2; (dipyridamole) 58-32-2; (lysine acetylsalicylate) 34220-70-7, 37933-78-1, 62952-06-1, 77337-52-1

L18 ANSWER 26 OF 30 SCISEARCH COPYRIGHT 2003 THOMSON ISI
AN 91:249298 SCISEARCH
GA The Genuine Article (R) Number: FH934
TI HEAT-CONDUCTIVITY AND SKIN TEMPERATURE AT THE TREATMENT OF ISCHEMIC-HEART-DISEASE WITH CURANTYL AND ISOPTIN
AU KOLLAR J (Reprint); UHRIK J; HEJJ F
CS PJ SAFARIKA UNIV, FAC MED, INST EXPTL MED, CS-04180 KOSICE, CZECHOSLOVAKIA (Reprint)
CYA CZECHOSLOVAKIA
SO INTERNATIONAL ANGIOLOGY, (1991) Vol. 10, No. 1, pp. 34-37.
DT Article; Journal
FS CLIN
LA ENGLISH
REC No References
Keyed

AB Forty one patients with ischaemic heart disease (IHD) of the age 60 +/- 12.3 years were hospitalized and treated two weeks with **Curantyl** (Dipyridamol) which was applied per os in a dose of 75 mg 3 times, and after another two weeks 34 of them wass applied Isoptin (Verapamil) in a dose of 40 mg 3 times daily. The heat conductivity (J.m-1, sec-1.degrees-C.10(-2), HC) and skin temperature (degrees-C, ST) were examined at the isothermic level 2 cm above the inner ankle by the

apparatus Fluvograph 2 of Hartmann and Braun A. G. (BRD). The HC after Isoptin application above the left and right ankle was in 34 patients increased significantly ($p < 0.001$). In patients with IHD after **Curantyl** application the HC and ST was significantly decreased above the left and right ankle in 9 (21.9%) and in 12 (30.0%), respectively. **Curantyl** could deteriorate HC and so to worsen legs **ulceration** healing and to point ap ischemia in patients with associated chronic postphlebitic syndrome with **ulcera** crurium.

CC CARDIOVASCULAR SYSTEM
ST Author Keywords: SKIN TEMPERATURE; HEAT CONDUCTIVITY

L18 ANSWER 27 OF 30 MEDLINE
AN 92177164 MEDLINE
DN 92177164 PubMed ID: 1795215
TI [Platelet antiaggregants].
Les antiagregants plaquettaires.
AU Verstraeten L; Francois P
CS Service de Biochimie medicale Cliniques Universitaires St-Luc, Bruxelles, Belgique.
SO JOURNAL DE PHARMACIE DE BELGIQUE, (1991 Jul-Aug) 46 (4) 261-5. Ref: 8
Journal code: 0375351. ISSN: 0047-2166.
CY Belgium
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA French
FS Priority Journals
EM 199204
ED Entered STN: 19920424
Last Updated on STN: 19920424
Entered Medline: 19920406
AB Antiplatelet agents are indicated in the prophylactic treatment of certain thromboses, and in particular those due to a complication of atherosclerosis. Acetylsalicylic acid is the best-known, the most commonly used and, probably, the currently most effective agent. The dosage remains controversial; yet, a mean dose of 300 mg daily appears to be recommended nowadays. Ticlopidine and, to a lesser extent, **dipyridamole** can also be used for this **treatment**. However numerous contra-indications, such as haemorragic diathesis, surgery and gastric **ulcers** tend to limit their use. As regards the combination of antiplatelet agents, clinical studies do not show superior efficacy as compared with acetylsalicyclic acid alone.
CT Check Tags: Animal; Human
English Abstract
*Platelet Aggregation Inhibitors: PD, pharmacology
Platelet Aggregation Inhibitors: TU, therapeutic use
CN 0 (Platelet Aggregation Inhibitors)

L18 ANSWER 28 OF 30 MEDLINE
AN 92182983 MEDLINE
DN 92182983 PubMed ID: 1797367
TI Atrophie blanche. A clinicopathological study of 27 patients.
AU Yang L J; Chan H L; Chen S Y; Kuan Y Z; Chen M J; Wang C N; Chen W J; Kuo T T
CS Department of Dermatology, Chang Gung Memorial Hospital, Taipei, Taiwan, R.O.C.
SO CHANG-KENG I HSUEH TSA CHIH, (1991 Dec) 14 (4) 237-45.
Journal code: 9809559.
CY TAIWAN: Taiwan, Province of China
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199204

ED Entered STN: 19920424
Last Updated on STN: 20000303
Entered Medline: 19920415

AB Twenty seven patients (8 males and 19 females) with atrophie blanche were observed in the past 7-years. The mean age at onset was 32 years (ranging from 23 years to 57 years) and 19 years (ranging from 11 years to 36 years) for male and female patient, respectively. The mean disease duration was 2.5 years (ranging from 2 months to 16 years) prior to their consultation. Sixty-three percent of them had summer exacerbation. Four patients had essential cryoglobulinemia, one of whom also developed bilateral iliofemoral artery stenosis one year later. Twelve patients also manifested concurrent purpura pigmentosa chronica (PPC)-like lesions. The observation of the natural course and clinical morphology, being divided into white atrophy-predominant and ulcer-predominant type, led to the impression that atrophie blanche and livedo vasculitis are synonyms with the same disease spectrum. Furthermore, white atrophy is not ulcer scars but lesions de novo suggesting dermal vasculopathy. An attempt was made to explain the uniqueness of clinical morphology. First line **treatment** included local **wound** care, bed rest and low-dose aspirin plus **dipyridamole**. Thirteen patients responded to these **treatment** either at the first attack or the recurrent episodes. Heparin (5000 units subcutaneous injection once daily) was effective for control of intractable painful **ulceration** in active stage in 70% of the remaining patients.

CT Check Tags: Female; Human; Male
Adolescent
Adult
Atrophy
Child
Leg Dermatoses: DT, drug therapy
*Leg Dermatoses: PA, pathology
Middle Age
Pigmentation Disorders: DT, drug therapy
*Pigmentation Disorders: PA, pathology
Telangiectasis: DT, drug therapy
*Telangiectasis: PA, pathology

L18 ANSWER 29 OF 30 MEDLINE
AN 91024230 MEDLINE
DN 91024230 PubMed ID: 2121103
TI Successful treatment of advanced gastric cancer with multiple liver metastasis by combination chemotherapy using mitomycin C, 5-fluorouracil, and high-dose leucovorin: a case report.
AU Nomura M; Nakano S; Kudou J; Ishibashi O; Niho Y
CS First Dept. of Internal Medicine, Faculty of Medicine, Kyushu University.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1990 Oct) 17 (10) 2097-100.
Journal code: 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 199011
ED Entered STN: 19910117
Last Updated on STN: 20000303
Entered Medline: 19901119

AB A 68-year-old woman complaining of severe iron deficiency anemia was found to have an advanced gastric cancer (poorly differentiated adenocarcinoma) with multiple liver metastases. The patients was **treated** three times with combination chemotherapy using a monthly schedule consisting of bolus infusion of mitomycin C (10 mg/m2) on day 1, continuous infusion of 5-fluorouracil (600 mg/m2) on day 1 to 6, and continuous infusion of high-dose leucovorin (300 mg/body) on day 1 to 6, with concomitant oral administration of **dipyridamole** (300 mg/day) over 14 days.

Endoscopically, cancerous **ulcer** in the primary gastric lesion improved like a healed peptic **ulcer**. Metastatic lesions in the liver almost disappeared on computed tomography. The most prominent side effect was oral mucositis which was tolerable and healed in a week. This regimen appears potentially useful in the treatment of gastric cancer.

CT Check Tags: Case Report; Female; Human
Adenocarcinoma: DT, drug therapy
*Adenocarcinoma: SC, secondary
Aged
*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
English Abstract
Fluorouracil: AD, administration & dosage
Leucovorin: AD, administration & dosage
Liver Neoplasms: DT, drug therapy
*Liver Neoplasms: SC, secondary
Mitomycin
Mitomycins: AD, administration & dosage
*Stomach Neoplasms: DT, drug therapy
Stomach Neoplasms: PA, pathology

RN 50-07-7 (Mitomycin); 51-21-8 (Fluorouracil); 58-05-9 (Leucovorin)

CN 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Mitomycins)

L18 ANSWER 30 OF 30 MEDLINE

AN 89134654 MEDLINE

DN 89134654 PubMed ID: 3224070

TI Therapy for isolated, low and high grade symptomatic carotid artery stenosis.

AU Fritz V U; Levien L J

CS Department of Neurology, Johannesburg Hospital, South Africa.

SO ANNALS OF VASCULAR SURGERY, (1988 Oct) 2 (4) 367-72.
Journal code: 8703941. ISSN: 0890-5096.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198903

ED Entered STN: 19900306
Last Updated on STN: 20000303
Entered Medline: 19890329

AB This study evaluates whether medical therapy alone can achieve satisfactory results in the treatment of low grade carotid stenosis or ulcerated plaques. Out of 525 patients presenting with transient or minor strokes, 64 were found with unilateral extracranial vascular disease as the sole potential source for their neurological symptoms. Utilizing arteriographic criteria, 35 patients with **ulcerated** plaques or carotid artery stenosis of less than 50% luminal artery diameter were **treated** conservatively with aspirin and **dipyridamole** (300 mg/day each). Twenty-nine patients with unilateral internal carotid artery stenosis of greater than 50% luminal artery diameter were **treated** by means of carotid endarterectomy. Follow-up in the two groups for a mean period of 24-26 months revealed no major strokes or neurological deaths in either group. Myocardial infarction was the major cause of death. Two patients developed subsequent transient ischemic attacks, and one a minor stroke with total recovery in the conservatively treated group. All became asymptomatic when warfarin replaced aspirin therapy. The findings in this study confirmed that "low grade" stenoses can be safely treated by medical measures alone.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Aged
*Brain Ischemia: SU, surgery
*Carotid Artery Diseases: SU, surgery
Cerebral Infarction: SU, surgery
Constriction, Pathologic: SU, surgery
*Endarterectomy: MT, methods

L7 ANSWER 21 OF 30 USPATFULL

AB A pharmaceutical composition of water, water soluble vinyl polymer gel, amine alcohol dispersant and IEP is used topically to treat herpes labialis and aphthous stomatitis lesions, and also to treat herpes genitalis, chicken pox, allergic conjunctivitis, giant papillary conjunctivitis, stomatitis secondary to chemotherapy, thermal burn, sunburn, and **decubitus** ulcers and shingles.

CLM What is claimed is:

1. A method for **treating** a disorder of the skin, mucous membranes, or conjunctival membranes comprising topically delivering an effective dose of histamine to a subject having said disorder, wherein said histamine is not histamine phosphate.

2. The method of claim 1, wherein said disorder is a viral disease selected from the group consisting of herpes labialis, herpes genitalis, herpes zoster, and varicella zoster.

3. The method of claim 1, wherein said disorder is selected from the group consisting of aphthous stomatitis, oral mucositis, allergic conjunctivitis, and giant papillary conjunctivitis.

4. The method of claim 1, wherein said disorder results from injury to the skin selected from the group consisting of photodermatitis, thermal burns, and **decubitus** ulcers.

5. The method of claim 1, wherein said histamine is administered in the form of a histamine precursor, wherein said histamine precursor is not histamine phosphate.

6. The method of claim 1, wherein said histamine is administered in the form of a histamine prodrug, and wherein said histamine prodrug is not histamine phosphate.

7. The method of claim 1, wherein said effective dose is administered through a unidose dispenser.

8. A composition comprising an effective dose of histamine in a pharmaceutically acceptable carrier adapted for topical delivery, wherein said histamine is present in a range from approximately 0.00325 to 0.0067 percent by weight, and wherein said histamine is not histamine phosphate.

9. The composition of claim 8, wherein said histamine is in the form of a histamine precursor, and wherein said histamine precursor is not histamine phosphate.

10. The composition of claim 8, wherein said histamine is in the form of a histamine prodrug, and wherein said histamine prodrug is not histamine phosphate.

11. The composition of claim 8, further comprising a neutralizer and an emulsifying agent.

12. The composition of claim 11, wherein said emulsifying agent is an amino alcohol.

13. The composition of claim 8, further comprising a pharmaceutically acceptable preservative.

14. The composition of claim 13, wherein said preservative is selected from the group consisting of propylparaben or methlyparaben.

15. The composition of claim 8, wherein said composition is in the form

of a lotion.

16. The composition of claim 8, wherein said composition is in the form of a gel.

17. The composition of claim 8, wherein said composition is in the form of a mouthwash.

18. A method for making a composition for the topical delivery of histamine comprising the steps of: providing a pharmaceutically acceptable carrier and histamine in a concentration from approximately 0.00325 to 0.0067 percent by weight, to **treat** a disorder of the skin selected from the group consisting of herpes labialis, herpes genitalis, herpes zoster, varicella zoster, aphthous stomatitis, oral mucositis, allergic conjunctivitis, giant papillary conjunctivitis, photodermatitis, thermal burns, and **decubitus** ulcers; and forming an emulsion containing the pharmaceutically acceptable carrier and the histamine, wherein said histamine is not histamine phosphate.

19. The method of claim 18, wherein said histamine is in the form of a histamine prodrug, and wherein said histamine prodrug is not histamine phosphate.

20. The method of claim 18, wherein said histamine is in the form of a histamine precursor, and wherein said histamine precursor is not histamine phosphate.

ACCESSION NUMBER:	2000:80403 USPATFULL		
TITLE:	Method and composition for topical treatment of damaged tissue using histamine as active ingredient		
INVENTOR(S):	Jack, Bruce A., Albuquerque, NM, United States White, B. Thomas, Albuquerque, NM, United States		
PATENT ASSIGNEE(S):	Maxim Pharmaceutical, Inc., San Diego, CA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6080395		20000627
APPLICATION INFO.:	US 1998-196840		19981120 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1998-20231, filed on 9 Feb 1998, now patented, Pat. No. US 5882639 which is a division of Ser. No. US 1996-691446, filed on 2 Aug 1996, now patented, Pat. No. US 5716610 which is a continuation of Ser. No. US 1994-199103, filed on 22 Feb 1994, now abandoned which is a continuation-in-part of Ser. No. US 1992-886304, filed on 21 May 1992, now patented, Pat. No. US 5294440 which is a continuation of Ser. No. US 1991-715410, filed on 14 Jun 1991, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Bawa, Raj		
LEGAL REPRESENTATIVE:	Knobbe, Martens, Olson & Bear, LLP		
NUMBER OF CLAIMS:	20		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1993		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 23 OF 30 USPATFULL

AB New uses for heparin, or heparin-like compounds are described that encompass preserving and healing of cells and cell functions arising from transplantations, circumcisions, dermatitides, fissures, fistulas, stimulation of epithelial growth, keloid prevention, cold injuries, pathology and forensic diagnosis, myocardium, trauma, **decubitus** ulcers, psoriasis, poisonings, insect and snake bites, corrosive ingestions, the "bends," space-travel sickness, brain and heart nerve conduction electrical dysrhythmias, pulmonary respiratory distress, blood and blood products, ulcerative colon lesions, interstitial cystitis, and related cosmetic uses. The uses are realized by applying the compounds either in solution, or in the for of a cream or aerosol, preferably at a pH of about 5.5, in an effective amount and for a time sufficient to effect treatment. Generally, the concentration of heparin or heparin-like compounds will be in the range of 1500 to 5000 international units per milliliter. Clinical assays are also described for determining the amount of heparin that should be used in those instances where the effective concentration is not known.

CLM What is claimed is:

1. A method for **treating** a patient having a lesion selected from the group consisting of circumcisions, injuries due to cold temperature exposure, fissures, fistulas, keloids and non-healing open necrotic ischemic skin lesions which comprises administering to said patient, at an acidic pH and for a time sufficient to effect **treatment** of said lesion, a pharmaceutically acceptable agent consisting essentially of an anticellular destructive chemical selected from the group consisting of heparin, heparinoids and heparin sulfate.

2. A method as in claim 1 wherein the adequacy of progress of initial **treatment** is indicated by termination of acute pain incurred by said patient from said lesion.

3. A method as in claim 1 wherein said agent is administered onto the surface of the affected organ at the site of said lesion.

4. A method as in claim 3 wherein said agent is administered 1-4 times per day in a concentration of 1,500-5,000 International Units per milliliter.

5. A method as in claim 1 wherein said agent is administered subcutaneously into normal non-involved subcutaneous fat tissue.

6. A method as in claim 5 wherein said agent is administered in a concentration of 5,000-80,000 International Units per milliliter.

7. A method as in claim 1 wherein said non-healing open necrotic ischemic skin lesion is a skin ulcer.

8. A method as in claim 7 wherein said skin ulcer is a **decubitus** ulcer.

9. A method as in claim 7 wherein said agent is administered topically to said skin ulcer.

10. A method as in claim 9 wherein said agent is administered in a concentration of 1,500-5,000 International Units per milliliter.

11. A method as in claim 1 wherein said injury due to cold temperature exposure is hypothermic injury or frostbite.

12. A method as in claim 11 wherein said agent is administered subcutaneously at the time of acute exposure.

13. A method as in claim 12 wherein said agent is administered in a concentration of 5,000-80,000 International Units per milliliter.

14. A method as in claim 11 wherein said agent is administered intravenously during later warming and thawing.

15. A method as in claim 14 wherein said agent is administered in a concentration of 5,000-20,000 International Units per milliliter.

16. A method as in claim 14 wherein the intravenous agent is administered at a rate sufficient to relieve the acute pain of said patient incident to said warming and thawing.

17. A method as in claim 16 wherein said administration is terminated when said pain is completely relieved.

18. A method as in claim 1 wherein said lesion is circumcision and said agent is administered to the circumcised penis prepuce.

ACCESSION NUMBER:	91:62773 USPATFULL		
TITLE:	Medical application for heparin and related molecules		
INVENTOR(S):	Saliba, Jr., Michael J., 5582 Thunderbird La., La Jolla, CA, United States 92037		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5037810		19910806
APPLICATION INFO.:	US 1989-412403		19890926 (7)
RELATED APPLN. INFO.:	Division of Ser. No. US 1987-27195, filed on 17 Mar 1987, now patented, Pat. No. US 4879282, issued on 7 Nov 1989		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Griffin, Ronald W.		
ASSISTANT EXAMINER:	Carson, Nancy S.		
LEGAL REPRESENTATIVE:	Brown, Martin Haller and McClain		
NUMBER OF CLAIMS:	18		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	23 Drawing Figure(s); 6 Drawing Page(s)		
LINE COUNT:	875		
CAS INDEXING IS AVAILABLE FOR THI			

L7 ANSWER 26 OF 30 USPATFULL

AB A decubital remedy suitable for cutaneous administration contains ubidecarenone as an effective ingredient. The decubital remedy, which may preferably take the form of a cream, lotion or ointment, is effective in reducing **decubitus**-related severe pain and restoring the tissue damaged by **decubitus**. It is applicable even to patients who are unable to take drugs orally by themselves due to dyscrasia or cranial nerve disorders. It is also free of such cumbersomeness and body-wide influence as injection.

CLM What is claimed is:

1. A method for the **treatment** of **decubitus** which comprises cutaneously applying to an affected area of a patient suffering therefrom an effective amount of ubidecarenone.

ACCESSION NUMBER:	88:55419 USPATFULL
TITLE:	Decubital remedy
INVENTOR(S):	Okuyama, Shinichi, 15-38 Nakayama 3-chome, Sendai-shi, Miyagi Prefecture, Japan Furuse, Kazumaro, 3-5, Inogashira 2-chome, Mitaka-shi, Tokyo, Japan Ohsawa, Shigemitsu, 2286-12, Suehiro-cho, Honjyo-shi, Saitama Prefecture, Japan

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4767624		19880830	
APPLICATION INFO.:	US 1986-838559		19860311	(6)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1985-50543	19850315

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Rollins, John
NUMBER OF CLAIMS:	1
EXEMPLARY CLAIM:	1
LINE COUNT:	347

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

collagen
dipyridamole: PD, pharmacology
dipyridamole: CM, drug comparison
malonaldehyde: EC, endogenous compound
maltol: CM, drug comparison
maltol: CB, drug combination
maltol: PD, pharmacology
ticlopidine: PD, pharmacology
ticlopidine: CM, drug comparison

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (adenosine diphosphate) 20398-34-9, 58-64-0; (aspalatone) 147249-33-0; (collagen) 9007-34-5; (dipyridamole) 58-32-2; (malonaldehyde) 542-78-9; (maltol) 118-71-8; (ticlopidine) 53885-35-1, 55142-85-3

CO Aldrich (United States); Sigma (United States); Chronolog (United States)

L18 ANSWER 5 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 5

AN 90209707 EMBASE

DN 1990209707

TI Gastric antiulcer and cytoprotective effects of dipyridamole in rats.

AU Tariq M.; Ageel A.M.

CS Department of Pharmacology, College of Pharmacy, King Saud University, P.O. Box 2457,Riyadh-11451, Saudi Arabia

SO Journal of Pharmacology and Experimental Therapeutics, (1990) 253/3 (944-949).
ISSN: 0022-3565 CODEN: JPETAB

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
048 Gastroenterology
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB **Dipyridamole** has been studied for its ability to inhibit gastric secretion and to protect gastric mucosa against the injuries caused by hypothermic restraint stress, indomethacin and various necrotizing agents including 80% ethanol, 0.6 M HCl, 0.2 M NaOH and 25% NaCl in rats. The results of this study demonstrate that **dipyridamole** has both prophylactic and curative effects on various experimentally induced gastric **ulcers**. It produced inhibition of normal and histamine-stimulated gastric secretion in rats. The intensity of gastric lesions induced by indomethacin and hypothermic restraint stress was reduced significantly by **dipyridamole**. Our findings also showed that **dipyridamole** protect gastric wall against hypothermic restraint stress-induced depletion. It produced marked cytoprotective effect against all the necrotizing agents used in this study. The cytoprotective effect of **dipyridamole** against 80% ethanol was reversed significantly by prior **treatment** with a dose of indomethacin that inhibits prostaglandin biosynthesis. These data indicate that **dipyridamole** inhibits the formation of gastric lesions by mucosal generation of prostaglandins. The concentration of nonprotein sulfhydryls were decreased significantly in gastric mucosa after administration of 80% ethanol. **Treatment** with **dipyridamole** replenish the reduced level of gastric mucosal nonprotein sulfhydryls, thus suggesting the mediation of its protective effect through sulfhydryls. Our findings show that **dipyridamole** possesses both antisecretory and antiulcer effects. Further studies are required to determine its role in the prophylaxis and or the **treatment** of gastric **ulcer** disease.

CT Medical Descriptors:
*cell protection
*stomach acid secretion
*stomach mucosa lesion

oral drug administration
female
Drug Descriptors:
*acetylsalicylic acid: DT, drug therapy
*dipyridamole: DT, drug therapy
*ticlopidine: DT, drug therapy
RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (ticlopidine) 53885-35-1, 55142-85-3

L18 ANSWER 7 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 7
AN 83214112 EMBASE
DN 1983214112
TI Thrombotic etiology of stress ulcers. I. The effect of anticoagulant and antiplatelet aggregators in the development of stress ulcers in rats.
AU Kumashiro R.; Pavlides C.A.; Kholoussy A.M.; Matsumoto T.
CS Dep. Surg., Hahnemann Med. Coll., Philadelphia, PA 19102, United States
SO American Surgeon, (1983) 49/8 (417-422).
CODEN: AMSUAW
CY United States
DT Journal
FS 037 Drug Literature Index
048 Gastroenterology
018 Cardiovascular Diseases and Cardiovascular Surgery
LA English
AB The preventative effect of anticoagulant (heparin) and antiplatelet aggregators (**dipyridamole**, low-dose aspirin, and ticlopidine), which are well known as antithrombotic agents, were recognized in this study of the development of stress **ulcers** in rats under cold restraint stress. On the basis of these findings, we suggest that the development of stress **ulceration** has a thrombotic etiology and that antiplatelet aggregators may be useful in the **treatment** of critically ill patients with stress **ulcers**.
CT Medical Descriptors:
*drug efficacy
*stomach ulcer
*stress ulcer
*thrombosis
etiology
rat
thrombocyte aggregation
stomach
nonhuman
blood and hemopoietic system
animal experiment
animal model
cardiovascular system
Drug Descriptors:
*acetylsalicylic acid
*dipyridamole
*heparin
*lysine acetylsalicylate
*ticlopidine
RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (dipyridamole) 58-32-2; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (lysine acetylsalicylate) 34220-70-7, 37933-78-1, 62952-06-1, 77337-52-1; (ticlopidine) 53885-35-1, 55142-85-3
CN Aspirin; Persantin; Venopirin
CO Robins (United States); Green cross (Japan); Boehringer ingelheim (Germany); Toulouse (France)

L18 ANSWER 8 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 8
AN 77075263 EMBASE
DN 1977075263
TI Interference on the haemostasis in dogs with induced coagulopathies by

CT Medical Descriptors:
*peripheral vascular disease: DM, disease management
*peripheral vascular disease: SU, surgery
*saphenous vein graft
*femoropopliteal bypass
clinical protocol
vein graft
allograft
bypass surgery
limb salvage
health care cost
cost effectiveness analysis
treatment outcome
postoperative complication: CO, complication
thromboembolism: CO, complication
thromboembolism: DT, drug therapy
thromboembolism: PC, prevention
graft rejection: CO, complication
graft rejection: DT, drug therapy
graft rejection: PC, prevention
human
male
female
clinical article
aged
adult
article
priority journal
Drug Descriptors:
*anticoagulant agent: DT, drug therapy
*immunosuppressive agent: DO, drug dose
*immunosuppressive agent: DT, drug therapy
*vasodilator agent: DT, drug therapy
azathioprine: DO, drug dose
azathioprine: DT, drug therapy
methylprednisolone: DT, drug therapy
cyclosporin A: DT, drug therapy
dextran
warfarin: DT, drug therapy
acetylsalicylic acid: DO, drug dose
acetylsalicylic acid: DT, drug therapy
heparin: DT, drug therapy
heparin: IV, intravenous drug administration
glyceryl trinitrate: DT, drug therapy
calcium channel blocking agent: DT, drug therapy
enoxaparin
RN (azathioprine) 446-86-6; (methylprednisolone) 6923-42-8, 83-43-2; (cyclosporin A) 59865-13-3, 63798-73-2; (dextran) 87915-38-6, 9014-78-2; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (glyceryl trinitrate) 55-63-0; (enoxaparin) 9041-08-1
CN (1) Rheomacrodex; (2) Coumadin; (3) Lovenox
CO (1) Mediscan (United States); (2) DuPont (United States); (3) Rhone Poulenc Rorer (United States); Lederle (United States); Burroughs Wellcome (United States); Sandoz (United States); Upjohn

L18 ANSWER 3 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 3
AN 96085854 EMBASE
DN 1996085854
TI Livedo vasculitis - Atrophie blanche.
AU Zorzi F.; Coggi A.
CS Institute of Dermatological Sciences, University of Milan, Via Pace 9,I-20122 Milan, Italy

SO European Journal of Dermatology, (1996) 6/2 (110-112).
ISSN: 1167-1122 CODEN: EJDEE4
CY France
DT Journal; Article
FS 013 Dermatology and Venereology
037 Drug Literature Index
LA English
SL English
AB Livedo vasculitis - atropine blanche, is a form of reticular livedo with recurrent episodes of **ulceration** leaving porcelain-like areas surrounded by a pigmented-telangiectatic halo. It may be idiopathic or may accompany different disorders. **Treatment** with vasodilators, anti-platelet agents, anticoagulants, steroids have been proposed. We describe a case where the typical cutaneous signs were accompanied by a serologic pattern suggestive (but not diagnostic) of lupus erythematosus (LES). A satisfactory improvement was obtained with pentoxifylline and **dipyridamole** plus steroids and acetyl-salicylic acid.
CT Medical Descriptors:
*livedo reticularis: DI, diagnosis
*livedo reticularis: DT, drug therapy
*systemic lupus erythematosus: DT, drug therapy
*vasculitis: DI, diagnosis
*vasculitis: DT, drug therapy
*vasculitis: CO, complication
adult
article
case report
clinical trial
female
human
human tissue
Drug Descriptors:
*dipyridamole: DT, drug therapy
*dipyridamole: CB, drug combination
*pentoxifylline: DT, drug therapy
*pentoxifylline: CB, drug combination
acetylsalicylic acid: DT, drug therapy
acetylsalicylic acid: CB, drug combination
methylprednisolone: DT, drug therapy
methylprednisolone: CB, drug combination
RN (dipyridamole) 58-32-2; (pentoxifylline) 6493-05-6; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (methylprednisolone) 6923-42-8, 83-43-2

L18 ANSWER 4 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 4
AN 95219538 EMBASE
DN 1995219538
TI Synthesis and antiplatelet effects of the new antithrombotic agent aspalatone with low ulcerogenicity.
AU Han B.H.; Suh D.-Y.; Yang H.Q.; Park Y.-H.; Kang Y.H.; Kim Y.C.
CS Natural Products Research Institute, Seoul National University, Yeongun-dong 28,Chongro-ku, Seoul 119-460, Korea, Republic of
SO Arzneimittel-Forschung/Drug Research, (1994) 44/10 (1122-1126).
ISSN: 0004-4172 CODEN: ARZNAD
CY Germany
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
048 Gastroenterology
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LA English
SL English; German

L50 ANSWER 22 OF 28 USPATFULL

DETD One example of a topical composition comprises 0.05 to 1% **sildenafil**, 75% (w/w) white petrolatum USP, 4% (w/w) paraffin wax USP/NF, lanolin 14% (w/w), 2% sorbitan sesquioleate NF, and 4% propylene glycol USP at the therapeutic effective dose to the anorectal area. Typically, the 50 mg to 600 mg of **sildenafil** ointment can be applied to the anorectal area in order to reduce the signs and/or symptoms associated with anorectal disorders, for example, anal fissure, anal **ulcers**, and hemorrhoidal diseases. The concentration of **sildenafil**, or other phosphodiesterase inhibitors can be varied by adjusting the ratio between the **sildenafil** with excipients facilitate either the attachment of **sildenafil** to the local tissue, or agents enhance absorption to the afflicted tissue.

PI US 6391869 B1 20020521

L63 ANSWER 21 OF 58 CAPLUS COPYRIGHT 2003 ACS
AN 1996:360289 CAPLUS
DN 125:55283
TI Matrix metalloproteinases, gelatinase and collagenase, in chronic leg ulcers
AU Weckroth, Miina; Vaheri, Antti; Lauharanta, Jorma; Sorsa, Timo; Konttinen, Yrjo T.
CS Haartman Institute, University of Helsinki, Helsinki, Finland
SO Journal of Investigative Dermatology (1996), 106(5), 1119-1124
CODEN: JIDEAE; ISSN: 0022-202X
PB Elsevier
DT Journal
LA English
CC 14-9 (Mammalian Pathological Biochemistry)
AB Although extracellular proteolysis is a prerequisite for normal wound healing, uncontrolled proteolytic tissue destruction appears to be a pathogenic factor in non-healing wounds. The aim of the study was to compare the activities of the serine proteinases of polymorphonuclear origin, elastase and cathepsin G, and the metalloproteinases, gelatinase and collagenase, in chronic leg ulcer exudate (10 patients) and acute **wound** fluid (6 patients). Serine proteinase activities were low in leg ulcer exudates but very high in some but not all acute **wound** fluids. Total collagenase activity, measured as activity against type I collagen monitored by SDS-PAGE and densitometry, was higher in chronic leg ulcer exudate than in acute **wound** fluid and its degree of autoactivation was relatively high. Doxycycline inhibition studies suggested that the collagenase activity in chronic leg **ulcer** exudate was MMP-1 ("fibroblast-type") and not MMP-8 ("neutrophil-type"). Zymog. **anal**. of the gelatinolytic enzymes in acute **wound** fluid showed a progressive increase from the day of operation to postoperative day 5, but the degree of activity was lower than in chronic leg **ulcer** exudate and the low mol. mass activation products were faint. The leg **ulcer** gelatinase profiles were characterized by high expression of 92/82- and 72/62-kDa duplex bands and by the presence of low mol. mass activation products. Leg ulcer collagenase seems to be derived from mononuclear rather than polymorphonuclear cells, which are known to be involved in acute **wound** healing. In conclusion, the present study shows that gelatinase and collagenase, but not elastase and cathepsin G are found in chronic leg ulcer exudate.
ST matrix metalloproteinase gelatinase collagenase leg ulcer
IT Exudate
Wound
(gelatinase and collagenase but not elastase and cathepsin G are found in chronic leg ulcer exudate in humans)
IT Leg
(disease, ulcer, gelatinase and collagenase but not elastase and cathepsin G are found in chronic leg ulcer exudate in humans)
IT Skin, disease
(ulcer, gelatinase and collagenase but not elastase and cathepsin G are found in chronic leg ulcer exudate in humans)
IT 9001-12-1, Collagenase 141907-41-7, Proteinase, matrix metallo-
146480-35-5, 72 KDA gelatinase 146480-36-6, 92 KDA gelatinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(gelatinase and collagenase but not elastase and cathepsin G are found in chronic leg ulcer exudate in humans)
IT 9004-06-2, Elastase 56645-49-9, Cathepsin G
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gelatinase and collagenase but not elastase and cathepsin G are found in chronic leg ulcer exudate in humans)

Trypanosoma brucei. TbPDE2A is a class I phosphodiesterase. Its catalytic domain exhibits 30-40% sequence identity with those of all 11 mammalian phosphodiesterase (PDE) families, as well as with PDE2 from Saccharomyces cerevisiae, dunce from Drosophila melanogaster, and regA from Dictyostelium discoideum. The overall structure of TbPDE2A resembles that of human PDE11A in that its N-terminal region contains a single GAF domain. This domain is very similar to those of the mammalian PDE2, -5, -6, -10, and -11, where it constitutes a potential cGMP binding site. TbPDE2A can be expressed in S. cerevisiae, and it complements and S. cerevisiae PDE deletion strain. Recombinant TbPDE2A is specific for cAMP, with a Km of .apprx.2 .mu.M. It is entirely resistant to the nonselective PDE inhibitor 3-isobutyl-1-methylxanthine, but it is sensitive to trequinsin, **dipyridamole**, sildenafil, and ethaverine with **IC50 values** of 5.4, 5.9, 9.4, and 14.2 .mu.M, resp. All four compds. inhibit proliferation of bloodstream form trypanosomes in culture, indicating that TbPDE2A is an essential enzyme.

IT **58-32-2**, **Dipyridamole** 486-47-5, Ethaverine
79855-88-2, Trequinsin 139755-83-2, Sildenafil
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors of Trypanosoma brucei cAMP-specific phosphodiesterase PDE2A)

L2 ANSWER 12 OF 14 USPATFULL

DETD A "therapeutically-effective dose" of the oligopeptides of the present invention will be an amount sufficient to diminish smooth muscle cell proliferation below a level associated with pathological events, such as restenosis, and yet allow adequate **wound** repair. Of course, the amount of the therapeutically- or prophylactically-effective compound which is actually administered will depend on the condition of the subject being **treated**, the nature and severity of the disease, the body weight, and also on the mode of administration, as well as the judgment of the attending physician. If desired, the oligopeptides may be co-administered with other agents, such as heparin, aspirin, **dipyridamole**, tissue plasminogen activator, streptokinase, urokinase, sulfinpyrazone, suloctidil, the peptide Arg-Gly-Asp-Ser, and/or antibodies reactive with the PDGF receptor.

PI US 5268358 19931207

L2 ANSWER 9 OF 14 USPATFULL

AB Agonists of the adenosine A.sub.2 receptor promote the migration of endothelial cells, fibroblasts and epithelial cells. Thus, methods and pharmaceutical compositions useful for **treating wounds** and promoting **wound** healing comprise agents which cause stimulation of the adenosine A.sub.2 receptor, preferably receptor agonists and adenosine uptake blockers. Preferred agonists include 2-phenylaminoadenosine, 2-para-2-carboxyethylphenyl-amino-5'N-ethylcarboxamidoadenosine, 5'N-ethylcarbox-amidoadenosine, 5'N-cyclopropyladenosine, 5'N-methyl-carboxamidoadenosine and PD-125944. Preferred uptake blockers include **dipyridamole**, nitrobenzylthio-inosine, dilazep and R75231.

PI US 5932558 19990803

L3 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 1999:282073 CAPLUS
DN 130:320863
TI Use of inhaled nitric oxide for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**
IN Zapol, Warren M.; Bloch, Kenneth D.; Rosenzweig, Anthony
PA The General Hospital Corporation, USA
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-12
ICS A61K009-72; A61K031-155; A61K031-195; A61K031-27; A61K031-52; A61K033-00; A61K033-08
CC 1-12 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9920251	A1	19990429	WO 1998-US22044	19981019
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2309038	AA	19990429	CA 1998-2309038	19981019
	AU 9911012	A1	19990510	AU 1999-11012	19981019
	AU 751853	B2	20020829		
	EP 1073416	A1	20010207	EP 1998-953702	19981019
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	ZA 9809550	A	19990721	ZA 1998-9550	19981020
PRAI	US 1997-62926P	P	19971021		
	US 1997-971003	A	19971114		
	WO 1998-US22044	W	19981019		

AB A method for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation** in a mammal includes identifying a mammal which has ischemia-reperfusion or is at risk for developing ischemia-reperfusion in a non-pulmonary tissue, and causing the mammal to inhale a therapeutically effective amt. of gaseous nitric oxide sufficient to diminish the ability of leukocytes or platelets to become activated in a manner that contributes to an inflammatory process at the site of the ischemia-reperfusion or **inflammation** in the non-pulmonary tissue, thereby lessening or preventing non-pulmonary ischemia-reperfusion injury in the mammal.
ST ischemia reperfusion injury nitric oxide; antiinflammatory nitric oxide; leukocyte platelet activation nitric oxide antiinflammatory
IT Leukocyte
Leukocyte
Platelet (blood)
(activation; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)
IT Artery
(angioplasty; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)
IT Artery
(atherectomy; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)
IT Artery

(coronary, angioplasty; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Artery
(coronary, bypass surgery; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Transplant and Transplantation
(heart; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Intestine, disease
(inflammatory; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Anti-inflammatory agents
Anti-ischemic agents
Antiarthritics
Cytotoxic agents
Dermatitis
Encephalitis
Fibrinolysis
Gout
Hepatitis
Surgery
Transplant and Transplantation
Transplant rejection
(inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Glucocorticoids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Reperfusion
(injury; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Hypotension
(ischemia-reperfusion injury from temporary; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Brain, disease
Heart, disease
Kidney, disease
(ischemia; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Transplant and Transplantation
(kidney; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Cell activation
Cell activation
(leukocyte; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Heart, disease
(myocarditis; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Anti-inflammatory agents
(nonsteroidal; inhaled nitric oxide and other compds. for lessening or

preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Cell activation
(platelet; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Brain, disease
(stroke; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Lupus erythematosus
(systemic; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Thyroid gland, disease
Thyroid gland, disease
(thyroiditis; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Heart
Kidney
(transplant; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Injury
(trauma, ischemia-reperfusion injury from; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT Blood vessel
(vascular interventional procedure; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT 50-78-2, Aspirin 58-32-2, Dipyridamole 58-55-9, Theophylline, biological studies 8001-27-2, Hirudin 8001-27-2D, Hirudin, analogs 9002-01-1, Streptokinase 9005-49-6, Heparin, biological studies 9039-53-6, Urokinase 9054-89-1, Superoxide dismutase 10102-43-9, Nitric oxide, biological studies 37762-06-4, Zaprinast 55142-85-3, Ticlopidine 139639-23-9, Tissue plasminogen activator 139639-23-9D, Tissue plasminogen activator, analogs **139755-83-2**, Sildenafil 168464-34-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

IT 9025-82-5, Phosphodiesterase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; inhaled nitric oxide and other compds. for lessening or preventing non-pulmonary ischemia-reperfusion injury or **inflammation**)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

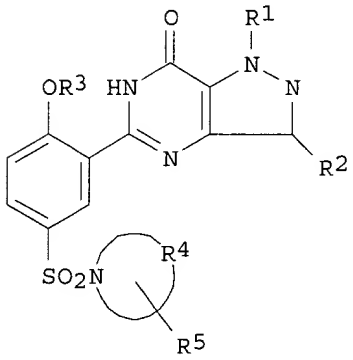
RE

(1) Frostell; US 5427797 A 1995 CAPLUS
(2) Garvey; US 5703073 A 1997 CAPLUS
(3) Zapol; US 5485827 A 1996
(4) Zapol; US 5570683 A 1996

L3 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2001:98405 CAPLUS
DN 134:141774
TI Methods, pharmaceutical compositions comprising cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors for prophylactic and treatment of diseases and conditions of the eye
IN Laties, Alan Malev
PA Pfizer Products Inc., USA
SO Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM A61K031-519
ICS A61P027-02; A61P027-06
CC 1-12 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1074258	A2	20010207	EP 2000-306235	20000721
	EP 1074258	A3	20010418		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2001048788	A2	20010220	JP 2000-222162	20000724
	US 2002119974	A1	20020829	US 2002-126375	20020419
PRAI	US 1999-146095P	P	19990728		
	US 2000-607562	B1	20000629		

OS MARPAT 134:141774
GI



I

AB The invention describes methods using cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors (I) [R1= H, C1-C3 alkyl, C3-C5 cycloalkyl, perfluoroalkyl; R2= H, (hydroxyl-substituted) C1-C6 alkyl, C3-C6 cycloalkyl, etc.; R3= C1-C6 alkyl, C3-C6 alkenyl, C3-C6 alkynyl, etc.; R4N completes pyrrolidinyl, morpholino, etc.; R5= H, C1-C4 alkyl, C1-C3 alkoxy, etc.] for prophylactic and therapeutic administration in patients with eye diseases and conditions including:central retinal artery occlusion; central retinal vein occlusion; optic neuropathy including, but not limited to, anterior ischemic optic neuropathy and glaucomatous optic neuropathy; and macular (dry) degeneration. Pharmaceutical compns. comprising cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors are also disclosed.

ST cyclic GMP phosphodiesterase inhibitor pharmaceutical eye disease
IT Glaucoma (disease)

(low-tension; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Eye, disease
(macula, degeneration, (dry); phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Nerve, disease
(neuropathy, optic; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Vein
(occlusion, central retinal; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Artery, disease
(occlusion, eye posterior ciliary body; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Heart, disease
(optic neuropathy assocd. with family history of; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Corticosteroids, biological studies
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optic neuropathy assocd. with intake of; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Surgery
(optic neuropathy assocd. with intraocular; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Diabetes mellitus
Hypertension
Inflammation
(optic neuropathy assocd. with; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Nerve
(optic, neuropathy, anterior ischemic and glaucomatous; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Antiglaucoma agents
Eye, disease
Glaucoma (disease)
(phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Eye, disease
(retina, ischemia, central retinal artery occlusion; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Blood pressure
(venous, glaucoma assocd. with episcleral; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

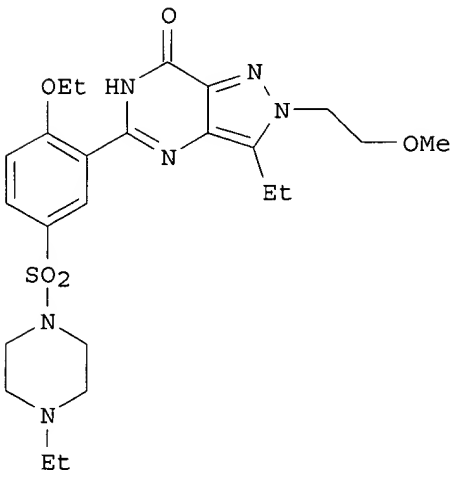
IT 139755-81-0 139755-82-1 **139755-83-2** 139755-84-3
139755-85-4 139755-86-5 139755-87-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT 9068-52-4, Cyclic guanosine 3',5'-monophosphate phosphodiesterase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(type 5; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

L3 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2001:525913 CAPLUS
DN 135:107336
TI Treatment of diabetic **ulcers** with pyrazolo[4,3-d]pyrimidine-7-one cGMP PDE5 inhibitors
IN Wood, Ralph E.; Davies, Michael John; Siegel, Richard Lewis
PA Pfizer Limited, UK; Pfizer Inc.
SO PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001051042	A2	20010719	WO 2001-IB18	20010111
WO 2001051042	A3	20020110		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1248623	A2	20021016	EP 2001-900568	20010111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI GB 2000-561	A	20000111		
WO 2001-IB18	W	20010111		

GI



I

AB This patent relates to the use of cyclic guanosine 3',5'-monophosphate phosphodiesterase type five (cGMP PDE5) inhibitors, including in particular the compd. sildenafil, for the treatment of diabetic **ulcers**, particularly diabetic foot **ulcers** (no data). I, a sildenafil analog, was prepd. in a multi-step sequence involving the amidation of 2-ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)-3-pyridinecarboxylic acid (prepn. given) with 4-amino-3-ethyl-1H-pyrazole-5-

carboxamide, addn. of 1-bromo-2-methoxyethane to the pyrazole ring, and cyclization using potassium bis(trimethylsilyl)amide and EtOAc in EtOH. Examples of formulations are included.

ST cyclic guanosine monophosphate phosphodiesterase inhibitor prepn diabetic **ulcer** treatment; cGMP PDE5 inhibitor prepn diabetic foot **ulcer** treatment

IT 171599-83-0, Sildenafil citrate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulation component; prepn. of pyrazolo[4,3-d]pyrimidin-7-one cGMP PDE5 inhibitors for treatment of diabetic **ulcers**)

IT 16250-08-1P, Pyridin-2-amino-5-sulfonic acid 247582-62-3P 247582-63-4P 247582-68-9P 247582-73-6P 264920-27-6P 350047-17-5P 350047-18-6P 350047-19-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of pyrazolo[4,3-d]pyrimidin-7-one cGMP PDE5 inhibitors for treatment of diabetic **ulcers**)

IT **139755-83-2P**, Sildenafil 334826-98-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); **USES (Uses)**
(prepn. of pyrazolo[4,3-d]pyrimidin-7-one cGMP PDE5 inhibitors for treatment of diabetic **ulcers**)

IT 504-29-0, 2-Aminopyridine 5308-25-8, 1-Ethylpiperazine 6482-24-2, 1-Bromo-2-methoxyethane 215298-74-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; prepn. of pyrazolo[4,3-d]pyrimidin-7-one cGMP PDE5 inhibitors for treatment of diabetic **ulcers**)

L3 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2001:780734 CAPLUS
DN 135:327353
TI Methods using a nitric oxide signaling pathway modulator for prevention and treatment of gastrointestinal disorders
IN Watkins, Crystal C.; Snyder, Solomon M.; Ferris, Christopher D.
PA Johns Hopkins University, USA
SO PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K045-00
CC 1-9 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001078781	A2	20011025	WO 2001-US12946	20010419
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002128171	A1	20020912	US 2001-840014	20010419
PRAI US 2000-198545P	P	20000419		

AB Methods are disclosed for preventing or treating a gastrointestinal (GI) disorder in a mammal, e.g. a human patient. In one embodiment, the methods include administering to the mammal a therapeutically effective amt. of a compd. that modulates a nitric oxide (NO) signaling pathway, particularly in GI neurons. Methods of the invention are particularly useful for the treatment (including prophylactic treatment) of diabetic gastropathies and other GI disorders.

ST gastrointestinal disease treatment NO pathway modulator; diabetic gastropathy treatment NO pathway modulator

IT Esophagus
(Barrett's syndrome; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Intestine, disease
(Crohn's; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Stomach, disease
(anacidity, gastrointestinal disorder assocd. with; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Appetite
(anorexia nervosa, gastrointestinal disorder assocd. with; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Intestine
(anus, anal fissure, gastrointestinal disorder assocd. with; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Appetite
(bulimia, gastrointestinal disorder assocd. with; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Intestine, disease
(colon, pseudoobstruction; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Intestine, disease

(constipation; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Stomach, disease
(diabetic gastropathy; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Digestive tract
(disease, achalasia, gastrointestinal disorder assocd. with; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Digestive tract
(disease, damage; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Gastrointestinal motility
(disorder, dysmotility; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Dyspepsia
Intestine, disease
(functional; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Digestive tract
(gastroesophageal reflux; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Surgery
(gastrointesintal damage from; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Diabetes mellitus
(gastrointestinal disorder assocd. with; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Drugs
(gastrointestinal; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Stomach, disease
(gastroparesis, idiopathic; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Esophagus
(hypo- or hypermotility; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Digestive tract
(indigestion; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Intestine
(interstitial cell of Cajal; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Intestine, disease
(irritable bowel syndrome, gastrointestinal disorder assocd. with; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Intestine, disease
(megacolon; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Nerve
(neuron, gastrointestinal; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)
IT Antidiabetic agents
Diarrhea
Domestic animal
Drug interactions
Gastric emptying
Nausea
Primate
Rabbit
Rodent
Signal transduction, biological
Vomiting

(nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Nerve
(nonadrenergic-noncholinergic, pyloric NANC relaxation; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Intestine, disease
(obstruction, pseudoobstruction; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Feeding
(postprandial discomfort; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Stomach
(pylorus, hypertrophic pyloric stenosis; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Digestive tract
(pyrosis; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Connective tissue
(scleroderma; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT Intestine, disease
(**ulcerative** colitis; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(and insulin-boosting agents; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT 9025-82-5, Phosphodiesterase 9068-52-4, CGMP phosphodiesterase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT 7665-99-8, Cyclic GMP
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(neuronal; nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT 68-94-0D, derivs. 114-07-8, Erythromycin 315-30-0D, derivs. 364-62-5, Metoclopramide 491-36-1D, 4(1H)-Quinazolinone, derivs. 2295-31-0D, Thiazolidinedione, derivs. 9004-10-8D, Insulin, variants, biological studies 13877-55-9D, derivs. 26078-04-6D, Purin-6-one, derivs. 57808-66-9, Domperidone 81098-60-4, Cisapride
139755-83-2 148871-66-3 148871-67-4 148871-68-5
148872-12-2 148872-13-3 148872-17-7 148872-25-7 148872-26-8
148872-27-9 150479-38-2 150479-39-3 150479-42-8 150479-52-0
150479-54-2 155879-56-4 155879-59-7 155879-61-1 155879-64-4
171599-83-0, Viagra
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

IT 10102-43-9, Nitric oxide, biological studies 125978-95-2, Nitric oxide synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(nitric oxide signaling pathway modulator for treatment of gastrointestinal disorders)

L3 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2002:31259 CAPLUS
DN 136:64173
TI Method using sildenafil or other cGMP phosphodiesterase 5 inhibitor for treating peripheral vascular diseases, peripheral neuropathies,and autonomic neuropathies
IN Wood, Ralph E.
PA USA
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-495
CC 1-12 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002002118	A1	20020110	WO 2001-US41202	20010629
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1303279	A1	20030423	EP 2001-957540	20010629
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2003105108	A1	20030605	US 2002-311907	20021219
PRAI	US 2000-215065P	P	20000630		
	US 2000-219029P	P	20000718		
	WO 2001-US41202	W	20010629		

AB A method is provided for treating a patient suffering from peripheral vascular disease, peripheral neuropathies, or autonomic neuropathies by administering a cGMP PDE5 inhibitor such as sildenafil. The method is particularly applicable to patients suffering from diabetic foot **ulcers**, Raynaud's Phenomenon, CREST Syndrome, erythromatosis, rheumatoid diseases, diabetic retinopathies and onychomycosis. According to the invention, a cGMP PDE5 inhibitor may be administered as a prophylactic to patients predisposed to develop a peripheral vascular disease, peripheral neuropathy, or autonomic neuropathy.

ST vascular peripheral disease cGMP phosphodiesterase 5 inhibitor; peripheral autonomic neuropathy cGMP phosphodiesterase 5 inhibitor; sildenafil vascular peripheral disease peripheral autonomic neuropathy

IT Blood vessel, disease
(Raynaud's phenomenon; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)

IT Nervous system
(autonomic, neuropathy; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)

IT Antiulcer agents
Diabetes mellitus
Foot
(diabetic foot **ulcer**; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)

IT Eye, disease
(diabetic retinopathy; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)

IT Disease, animal
(erythromatosis; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Nail (anatomical)
(onychomycosis; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Nerve, disease
(peripheral neuropathy; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Blood vessel, disease
(peripheral; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Rheumatic diseases
(rheumatoid disease; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Connective tissue
(scleroderma, CREST syndrome variant; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Drug delivery systems
Fungicides
(sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT 9068-52-4, Phosphodiesterase V
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT **139755-83-2**, Sildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bombrun; US 6043252 A 2000 CAPLUS
(2) Graham; US 6075028 A 2000 CAPLUS

L3 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2002:31259 CAPLUS
DN 136:64173
TI Method using sildenafil or other cGMP phosphodiesterase 5 inhibitor for treating peripheral vascular diseases, peripheral neuropathies,and autonomic neuropathies
IN Wood, Ralph E.
PA USA
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-495
CC 1-12 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002002118	A1	20020110	WO 2001-US41202	20010629
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1303279	A1	20030423	EP 2001-957540	20010629
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2003105108	A1	20030605	US 2002-311907	20021219
PRAI	US 2000-215065P	P	20000630		
	US 2000-219029P	P	20000718		
	WO 2001-US41202	W	20010629		

AB A method is provided for treating a patient suffering from peripheral vascular disease, peripheral neuropathies, or autonomic neuropathies by administering a cGMP PDE5 inhibitor such as sildenafil. The method is particularly applicable to patients suffering from diabetic foot **ulcers**, Raynaud's Phenomenon, CREST Syndrome, erythromatosis, rheumatoid diseases, diabetic retinopathies and onychomycosis. According to the invention, a cGMP PDE5 inhibitor may be administered as a prophylactic to patients predisposed to develop a peripheral vascular disease, peripheral neuropathy, or autonomic neuropathy.

ST vascular peripheral disease cGMP phosphodiesterase 5 inhibitor; peripheral autonomic neuropathy cGMP phosphodiesterase 5 inhibitor; sildenafil vascular peripheral disease peripheral autonomic neuropathy

IT Blood vessel, disease
(Raynaud's phenomenon; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)

IT Nervous system
(autonomic, neuropathy; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)

IT Antiulcer agents
Diabetes mellitus
Foot
(diabetic foot **ulcer**; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)

IT Eye, disease
(diabetic retinopathy; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)

IT Disease, animal
(erythromatosis; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Nail (anatomical)
(onychomycosis; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Nerve, disease
(peripheral neuropathy; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Blood vessel, disease
(peripheral; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Rheumatic diseases
(rheumatoid disease; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Connective tissue
(scleroderma, CREST syndrome variant; sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT Drug delivery systems
Fungicides
(sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT 9068-52-4, Phosphodiesterase V
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
IT **139755-83-2**, Sildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(sildenafil or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic neuropathies)
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bombrun; US 6043252 A 2000 CAPLUS
(2) Graham; US 6075028 A 2000 CAPLUS

L3 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS
AN 2002:157565 CAPLUS
DN 136:205425
TI Treatment of **wounds** with cyclic guanosine 3',5'-monophosphate phosphodiesterase type five inhibitors
IN Davies, Michael John; Huggins, Jonathan Paul; Parums, Dinah Velta
PA Pfizer Limited, UK; Pfizer Inc.
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002015893	A2	20020228	WO 2001-IB1470	20010816
	WO 2002015893	A3	20030313		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002065286	A1	20020530	US 2001-927344	20010810
	AU 2001076636	A5	20020304	AU 2001-76636	20010816
	EP 1311252	A2	20030521	EP 2001-954296	20010816
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	GB 2000-20588	A	20000821		
	US 2000-232669P	P	20000915		
	WO 2001-IB1470	W	20010816		

AB This invention relates to the use of cyclic guanosine 3', 5'-monophosphate phosphodiesterase type five (cGMP PDE5) inhibitors (hereinafter PDE5 inhibitors), including in particular the compd. sildenafil, for the treatment of chronic **wounds** of a non-diabetic origin including in particular chronic venous **ulcers**, chronic decubitus (pressure sores) and arterial **ulcers**; and acute **wounds**. Tablets were prepd. contg. sildenafil citrate.

ST **wound** healing cGMP phosphodiesterase inhibitor; sildenafil **wound** healing

IT Drug delivery systems
(oral; treatment of **wounds** with cyclic guanosine 3',5'-monophosphate type five inhibitors)

IT Drug delivery systems
(topical; treatment of **wounds** with cyclic guanosine 3',5'-monophosphate type five inhibitors)

IT **Wound** healing promoters
(treatment of **wounds** with cyclic guanosine 3',5'-monophosphate type five inhibitors)

IT 9004-06-2, Matrix metalloproteinase-12 79955-99-0, Matrix metalloproteinase-3 141907-41-7, Matrix metalloproteinase 175449-82-8, Matrix metalloproteinase-13
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; treatment of **wounds** with cyclic guanosine 3',5'-monophosphate type five inhibitors)

IT **139755-83-2**, Sildenafil 171599-83-0, Sildenafil citrate
RL: THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(treatment of **wounds** with cyclic guanosine 3',5'-monophosphate type five inhibitors)

IT 9068-52-4, CGMP phosphodiesterase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type 5 inhibitors; treatment of **wounds** with cyclic guanosine 3',5'-monophosphate type five inhibitors)

IT 9039-53-6, Urokinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type, PAI; treatment of **wounds** with cyclic guanosine 3',5'-monophosphate type five inhibitors)

IT 105844-41-5, Plasminogen activator inhibitor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(urokinase-type; treatment of **wounds** with cyclic guanosine 3',5'-monophosphate type five inhibitors)

L8 ANSWER 3 OF 3 USPATFULL
ACCESSION NUMBER: 97:12494 USPATFULL
TITLE: Method for inhibiting metalloproteinase expression
INVENTOR(S): Kohn, Elise C., Olney, MD, United States
Liotta, Lance A., Potomac, MD, United States
PATENT ASSIGNEE(S): The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5602156		19970211
APPLICATION INFO.:	US 1994-209089		19940310 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-122277, filed on 17 Sep 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: McKane, Joseph
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew LLP
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 796
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Calcium homeostasis is an important regulator of **MMP**-2 transcription, activation and activity. Disclosed herein are compounds which inhibit the expression of matrix metalloproteinases in cells. Pharmaceutical application of these compounds to inhibit the expression of **MMPs** offers a new approach to cancer treatment as well as treatment for nerve healing, degenerative cartilagenous diseases, **decubitus** ulcers, arthritis, Alzheimer's disease, wound healing, proliferative retinopathy, proliferative renal diseases, corneal ulcers and fertility problems.

SUMM One example of ectopic activity of an otherwise normal function is collagenolytic degradation of basement membrane and extracellular matrix by secreted matrix metalloproteinases (**MMPs**).

SUMM Proteolysis and interruption of the basement membrane requires activation of specialized matrix metalloproteinases which selectively degrade basement membrane collagens type IV and V, the type IV collagenases or gelatinases (**MMPs**). Liotta, et al., Nature 284:67-68 (1980). Two species of **MMPs**, the 72 kDa species (**MMP**-2, gelatinase A) and the 92 kDa species (**MMP**-9, gelatinase B) have been isolated, cloned and sequenced. Liotta, et al., ibid.; and Liotta, et al., Biochemistry 20:100-104 (1981). Both **MMPs** are secreted as latent proenzymes which require the removal of an 80 or 87 amino acid amino-terminal domain for activation. Stefler-Stevenson, et al., J. Biol Chem. 264:1353-1356 (1989). Little is known about the signaling pathways which mediate the production and activation of these enzymes. While the activity of these proteinases is metal ion (Zn.sup.++)-dependent, the regulation of **MMP** production by divalent cations is unknown.

SUMM Recent studies have focused on the induction and activation of **MMPs**. Others have demonstrated that stable transfection of primary rat embryo fibroblast cells with activated Ha-ras resulted in the metastatic phenotype and increased production of type IV collagenases; this result was abrogated by simultaneous transfection of adenovirus E1A with Ha-ras (Pozzatti, et al., Science. 23:223-227 (1986)). Similar results were seen when Ha-ras was transfected into human bronchial epithelial cells (Collier, et al., J. Biol. Chem. 263:6579-6587 (1988)). Further investigation into the induction and subsequent regulation of **MMP**-2 demonstrated coordinate

regulation of **MMP**-2 expression and function by treatment of human melanoma and fibrosarcoma cells with transforming factor-.beta..sub.1 (TGG-.beta..sub.1), 12-O-tetradecanoylphorbol-13-acetate (TPA), interleukin-1 (IL-1), and retionic acid (RA). See, Brown, et al., Cancer Research 50:6184-6191 (1990). TGF-.beta..sub.1 treatment resulted in induction of **MMP**-2 and inhibition of the interstitial collagenase, **MMP**-1. Conversely, TPA treatment produced inhibition of **MMP**-2 with induction of **MMP**-1. These results suggested involvement of transcriptional regulation and protein kinase C second messenger signaling pathways in the production of **MMP**-2. To date, there has been no demonstration of calciumdependent regulation of **MMP**-2 production or activation.

SUMM Compound 1, shown below, is a novel calcium influx inhibitor with antiproliferative and antimetastatic activities (Kohn, et al., J. Natl. Cancer Inst. 82:54-60 (1990); Felder, et al., J. Pharm. Exp. Therapeut. 257:967-971 (1991); and Kohn, et al., Cancer Res. 52:3208-3212 (1992)). Investigation into the mechanism of action of compound 1 has demonstrated that it inhibits receptor-operated and voltage-gated calcium influx (Felder, et al., J. Pharm. Exp. Therapeut. 257:967-971 (1991); Hupe, et al., J. Biol. Chem. 266:10136-10142 (1991)), calcium-dependent arachidonic acid release (Felder, et al., J. Pharm. Exp. Therapeut. 257:967-971 (1991); Clark, et al., Cell. 65:1043-1051 (1991)) and tyrosine phosphorylation with activation of phospholipase C-.gamma. (Gusovsky, et al., J. Biol. Chem. 268:7768-7772 (1993)). These functions could also be inhibited by compound 2, shown below, a chemically different inhibitor of receptor operated calcium channels. See, Gusovsky, et al., J. Biol. Chem. 268:7768-7772 (1993); Merritt, et al., J. Biol. Chem 271:515-522 (1990). This confirmed the role of compound 1-mediated inhibition of calcium influx on these biochemical events. The ability of compound 1 to inhibit selected calcium-mediated signal transduction pathways made it an ideal tool with which to investigate the role of calcium regulation underlying the expression and activation of **MMP**-2. ##STR1##

SUMM It has now been discovered that calcium homeostasis is an important regulator of **MMP**-2 transcription, activation and activity, and that certain compounds inhibit the expression of matrix metalloproteinases in cells. This invention provides a method for using compound 1 and related compounds to inhibit the expression of **MMPs** in cells.

SUMM Pharmaceutical application directed to inhibiting the expression of **MMPs** offers a new approach to cancer treatment as well as treatment for nerve healing, degenerative cartilagenous diseases, decubitus ulcers, arthritis, Alzheimer's disease, wound healing, proliferative retinopathy, proliferative renal diseases, corneal ulcers and fertility problems.

DRWD FIG. 1 shows several zymograms which illustrate the dose-dependent inhibition of **MMP**-2 gelatinase activity by compound 1 as well as the inhibition exhibited by several analogs of compound 1 as well as compound 2.

DRWD FIG. 2 shows the quantitation of compound 1 effects on **MMP**-2 gelatinase activity measured by laser densitometry of the zymograms in FIG. 1.

DRWD FIG. 4 is a Western immunoblot which confirms the dose-dependent of **MMP**-2 production in A2988 and HT1080 cells by compound 1.

DRWD FIG. 7 is a Northern blot showing the effect of compound 1 on the expression of **MMP**-1 and **MMP**-2 in A2058 cells.

DRWD The following abbreviations are used herein: **MMP**, matrix metalloproteinase; TGF-.beta..sub.1, transforming growth factor-.beta..sub.1 ; TIMP-2, tissue inhibitor of metalloproteinase-2;

DMEM, Dulbecco's modified Eagle's medium; EDTA, ethylenediamine tetraacetic acid; EGTA, ethylenebis(oxyethylenenitrilo)tetraacetic acid; DMSO, dimethyl sulfoxide; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

DRWD In further embodiments, this invention provides a method for inhibiting the expression of **MMP**-2 in a cell.

DETD A2058 human melanoma cells, human HT1080 fibrosarcoma cells, and OVCAR3 human ovarian cancer cells were incubated with increasing concentrations of compound 1 (0.2-20 .mu.M) or DMSO control (0.05%) and subjected to gelatin zymography. Aliquots of conditioned medium (15 .mu.L) were electrophoresed on gelatin-containing 10% PAGE gels under nonreducing but denaturing conditions. These conditions allow the different gelatin-degrading species (**MMPs**) to separate by size. The enzymes renature after removal of the SDS by incubation of the gel with 2.5 % Triton X-100, and degrade the gelatin substrate present in the polyacrylamide gel upon overnight incubation in low salt collagenase buffer. Bands of clearing, seen after Coomassie blue staining correspond to areas of gelatinase activity.

DETD Known concentrated conditioned medium from HT1080 cells was used for identification of the gelatinase species as marked in FIG. 1A: 92 kDa, gelatinase B/**MMP**-9; 72 kDa, gelatinase A/**MMP**-2 latent form; 65 kDa intermediate and 62 kDa activated forms of **MMP**-2. The activated form of **MMP**-2 results from cleavage of the amino terminal domain.

DETD Treatment of the three different human cancer cell lines with compound 1 resulted in a dose dependent reduction of **MMP** activity. A shift to activated species with subsequent decrease in total activity was seen for the HT1080 cell line. Quantitation of the zymograms in FIGS. 1A-1C were carded out using laser densitometry. The results were normalized to DMSO control lanes and are presented in FIG. 2. A greater than 80% reduction in activity of all **MMP**-2 species was seen for all cell lines. Treatment with 20 .mu.M compound 1 caused an almost complete reduction of activated **MMP**-2 in the A2058 and OVCAR3 cell lines, but only a 75 % reduction of the HT1080 line.

DETD Treatment of A2058 cells with compound 2 provided further correlation of calcium regulation with **MMP**-2 activity. Compound 2 is structurally dissimilar to compound 1 but is an effective inhibitor of receptor-operated calcium channels with reactivity against some voltage-gated calcium channels. It has been shown to have identical effects as compound 1 in receptor-operated calcium influx. See, Gusovsky, et al., J. Biol. Chem. 268:7768-7772 (1993). FIG. 1E shows a zymogram resulting from the treatment of A2058 cells with 0.05 % DMSO (control, lane 1), 10 .mu.M compound 1 (lane 2) and 10 .mu.M compound 2 (lane 3). Both compound 1 and compound 2 reduced **MMP**-2 activity.

DETD Gelatin zymography was carded out using control conditioned media from A2058 cells and HT1080 cells in the absence of compound 1. Zymogram slices were incubated in low salt collagenase buffer with control (DMSO 0.1%), an inhibitory dose of compound 1 (20 .mu.M), or the calcium chelators EGTA (10 mM) and EDTA (10 mM). Inclusion of EDTA in the incubation buffer has been shown by others to inhibit gelatinolytic activity. See, Brown, et al., Cancer Res. 50:6184-6191 (1990). FIG. 3 shows the control (A) and compound 1-treated (B) portions of the zymogram along with known concentrated conditioned medium from HT1080 cells which was used for identification of the gelatinase species (as in Example 1). Lane 1 for each of the zymograms corresponds to A2058 while lane 2 corresponds to HT1080. Incubation of the enzymes with compound 1 at concentrations which reduce **MMP**-2 activity from cell-derived conditioned media did not effect its activity in isolation. The results with EGTA and EDTA (not shown) confirmed the requirement for metal ion (Ca.sup.++) in the activation buffer and further confirmed that the mechanism of action of compound 1 reduction is not due to calcium chelation.

DETD The lack of reduction of gelatinolytic activity in conditioned medium by

compound 1 suggested that the effect of compound 1 on **MMP**-2 occured biochemically at the level of enzyme production or above.

DETD Effect of Compound 1 on the Presence of **MMP**-2 and Its Activated Species

DETD This example illustrates the dose-dependent effects of compound 1 on the presence of **MMP**-2 and its activated species. Western immunoblots were used to detect the effect of compound 1 on the presence of **MMP**-2 and its activated species and for crude quantitation of **MMP**-2 presence.

DETD A2058 and HT1080 conditioned media samples were concentrated 10-fold using ultrafiltration units excluding material of less than 10 or 30 kDa in molecular weight. Aliquots of 15 .mu.L were electrophoresed on 4-20% gradient PAGE gels, electrically transferred to membranes and immunoblotted with specific polyclonal antibody to proMMP-2. This antibody, made to the **MMP**-2/TIMP-2 complex recognizes the latent and activated **MMP**-2 species and crossreacts with TIMP-2 (21 kDa).

DETD Compound 1 caused a dose-dependent reduction of the presence of the **MMP**-2 species (FIG. 4). This reduction included a shift to the lower molecular weight activated species before more complete reduction of all species was seen after incubation with 20 .mu.M compound 1. This data suggests that compound 1 may have a selective effect on the production of **MMP**-2 by the tumor cells.

DETD Effect of Compound 1 and TGF-.beta..sub.1 on Gelatinase Activity and Presence of **MMPS**

DETD TGF-.beta..sub.1 has been shown to stimulate production of **MMP** -2 by stimulation of RNA expression. The effect of compound 1 on TGF-.beta..sub.1 -stimulated **MMP**-2 production was evaluated in A2058 and HT1080 cell lines.

DETD A2058 and HT1080 cells were incubated with compound 1 (2 .mu.M), with or without TGF-.beta..sub.1 (5 ng/mL) for 24 and 48 hours prior to harvest of conditioned media. Aliquots were subjected to gelatin zymography as described in Example 1. Known concentrated conditioned medium from HT1080 cells was used for identification of the gelatinase species (92 kDa, gelatinase B/**MMP**-9; 72 kDa, gelatinase A/**MMP**-2 latent form; 65 kDa intermediate and 62 kDa activated forms of **MMP**-2). FIG. 5 shows the results of these treatments for A2058 (5A) and HT1080 (5B).

DETD Compound 1 reduction of gelatinase activity increased from 24 to 48 hr exposure (FIG. 5, lanes 1-3). TGF-.beta..sub.1 increased gelatinase activity when used alone for 48 hr (lane 4). This increase was inhibited by co-incubation for 48 hr with compound 1 (lane 6). However, 48 hr exposure of the cells to TGF-.beta..sub.1 with addition of compound 1 over the final 24 hr showed little effect due to compound 1. These results suggest that compound 1 must be present during induction of **MMP**-2 transcription by TGF-.beta..sub.1 (first 24 hours) for compound 1 to inhibit the effects of TGF-.beta..sub.1 and suggest that compound 1 also may have an effect on **MMP**-2 transcription. Table 2 provides a densitometric analysis of the effect of compound 1 and TGF-.beta..sub.1 on Type IV collagenase species.

DETD TABLE 2

Densitometric Analysis of the Effect of Compound 1 and TGF-.beta..sub.1 on Type IV collagenase species

A. A2058 **MMP**-2 species.

	72 kDa TGF-.beta..sub.1		65 + 62 kDa TGF-.beta..sub.1	
Exposure (hr) to Compound 1 (2 .mu.M)	-	+	-	+
0	100*	68	100	0
24	84	44	14	0

48		45	36	0	0	

B. HT1080 **MMP**-2 and **MMP**-9 species.

Exposure (hr) to	92 kDa		72 kDa		65 + 62 kDa	
Compound 1	TGF-.beta.		TGF-.beta.		TGF-.beta.	
(2 .mu.M)	-	+	-	+	-	+
0	100	64	100	47	100	192
24	73	78	10	52	125	194
48	12	14	0.6	10	24	116

*The control band was defined as 100% gelatinase activity and the other bands were normalized to it. Numbers reflect triplicate measurements from each zymogram band of representative zymograms. Standard deviations, not shown, were .ltoreq.10%.

DETD To confirm that these results were due to the reduction of **MMP**-2, conditioned media samples from experiments shown in FIG. 5 were concentrated 10-fold and electrophoresed. The samples were electrically transferred to membranes, and immunoblotted with specific polyclonal antibody to proMMP-2/TIMP-2 complex as described in Example 3. The results are shown in FIGS. 6A (HT1080) and 6B (A2058). Prestained molecular weight markers are shown to the left and lanes are as described above for FIG. 5. As for the gel zymograms above, FIGS. 6A and 6B show that compound 1 inhibits **MMP**-2 in a time-dependent manner and must be present during induction of **MMP**-2 by TGF-.beta..sub.1 to inhibit its effects.

DETD The Effect of Compound 1 on Transcription of **MMP**-2

DETD This example illustrates the effect of compound 1 on **MMP**-1 and **MMP**-2 mRNA from A2058 cells using Northern blot analysis.

DETD Total cytoplasmic RNA was purified from A2058 cells using cesium chloride density centrifugation. Cells were treated with DMSO vehicle (0.05 %) or compound 1 (2 .mu.M) for 24 or 48 hr. Total RNA yields from treated and control cells (.mu.g/10.sup.6 cells) were similar. Aliquots (5 .mu.g) of total RNA were denatured and separated on formaldehyde-1% agarose slab gels, passively transferred to GeneScreen, and crosslinked using ultraviolet light exposure. RNA was hybridized in buffer (50% deionized formamide, 5x SSC, 10 mM Tris HCl pH 7.5, 1x Denharts solution without albumin, 1.0% SDS, and 0.125 mg/mL salmon sperm DNA) containing 10.sup.6 counts/mL of .sup.32 P- labeled probe of either **MMP**-2, **MMP**-1, or with GAPDH which was used as a measure of RNA load. Probes were labeled to high specific activity with .sup.32 P-dCTP using a random primer labeling protocol. The cDNA probes for the **MMP**-2, **MMP**-1, and GAPDH have been described. See, Brown, et al., Cancer Res. 50:6184-6191 (1990); Templeton, et at., Cancer Res. 50:5431-5437 (1990); and Fort, et al., Nucleic Acids Res. 13:1431-1441 (1985). Radiolabeled bands were quantitated using laser densitometric analysis of autoradiography bands. Numeric data are presented as percent inhibition of IVase or interstitial collagenase expression corrected for loading using GAPDH.

DETD FIG. 7A shows transferred RNA which was hybridized with .sup.32 P-labeled cDNA for **MMP**-2. The RNA was prepared from A2058 cells incubated with 0.1% DMSO (lane 1), compound 1 for 24 hrs (lane 2) or compound 1 for 48 hrs (lane 3). A greater than 50% inhibition in **MMP**-2 transcription by treatment with compound 1 is demonstrated at 24 and 48 hr (corrected for loading). These data confirm that compound 1 inhibits collagenolytic function by inhibition of transcription of **MMP**-2.

DETD FIG. 7B shows similar results using .sup.32 P-labeled cDNA for **MMP**-1.

DETD These results show that compound 1 inhibits the expression of interstitial collagenase **MMP**-1 and type IV collagenase/gelatinase A **MMP**-2.

CLM What is claimed is:

1. A method of inhibiting expression of matrix metalloproteinase in a host afflicted with a disease associated with overexpression of matrix metalloproteinase, comprising treating said host with an effective amount of a compound of formula: Y--(CH.sub.2).sub.p --Ar.sup.1 --X--Ar.sup.2 (I) wherein: is an integer of from 0 to 4; Ar.sup.1 and Ar.sup.2 are each aromatic moieties independently selected from the group consisting of phenyl, naphthyl, and substituted versions thereof; X is a linking moiety selected from the group consisting of O, S, SO.sub.2, CO, CHCN, straight chain alkyl, alkoxy, and alkoxyalkyl; and Y is a nitrogen-containing heterocyclic moiety selected from the group consisting of: radicals of the formula ##STR5## wherein: A is N or CH, R.sup.1 is a member selected from the group consisting of hydrogen, --CONH.sub.2, --CONHR.sup.5, --CO.sub.2 H, --CO.sub.2 R.sup.5, --SO.sub.2 NH.sub.2, R.sup.2 is a member selected from the group consisting of hydrogen, amino, --NHCOC.sub.6 H.sub.5, --NHCOR.sup.5, --NHCHO, --NHR.sup.5, --N(R.sup.5).sub.2 and R.sup.5 is lower alkyl of from 1 to 6 carbon atoms, and (b) 1,2,4-triazolyl, pyrazinyl, purinyl, pyrimidinyl, 1,2,3-triazolo-{4,5-d}-pyrimidinyl, and substituted versions thereof; said disease being a member selected from the group consisting of nerve disorders, degenerative cartilagenous diseases, **decubitus** ulcers, arthritis, Alzheimer's disease, wound healing, corneal ulcers and fertility problems.

12. A method in accordance with claim 1 wherein said matrix metalloproteinase is **MMP**-2.

13. A method in accordance with claim 1 wherein said matrix metalloproteinase is **MMP**-1.

(FILE 'HOME' ENTERED AT 19:03:34 ON 03 OCT 2002)

FILE 'USPATFULL' ENTERED AT 19:03:50 ON 03 OCT 2002
L1 166 S DECUBITUS/CLM OR (VENOUS ULCER? OR ATERIAL ULCERS)/CLM
L2 142 S DECUBITUS/AB OR (VENOUS ULCER? OR ATERIAL ULCERS)/AB
L3 72 S L1 AND L2
L4 72 FOCUS L3 1-
L5 184352 S TREAT?/CLM
L6 30 S L5 AND L3
L7 30 FOCUS L6 1-

=> s l3 and (PDE? or MMP?)
L8 3 L3 AND (PDE? OR MMP?)

=> d 1-3 ibib,hit,

L8 ANSWER 1 OF 3 USPATFULL
ACCESSION NUMBER: 2002:126769 USPATFULL
TITLE: Treatment of wounds
INVENTOR(S): Davies, Michael John, Sandwich, UNITED KINGDOM
Huggins, Jonathan Paul, Sandwich, UNITED KINGDOM
Parums, Dinah, Sandwich, UNITED KINGDOM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002065286	A1	20020530
APPLICATION INFO.:	US 2001-927344	A1	20010810 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2000-20588	20000821
	US 2000-232669P	20000915 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159, Eastern Point Road, Groton, CT, 06340
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 585
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the use of cyclic guanosine 3', 5'-monophosphate type five (cGMP **PDE5**) inhibitors (hereinafter **PDE5** inhibitors), including in particular the compound sildenafil, for the treatment of chronic wounds of a non-diabetic origin including in particular chronic **venous ulcers**, chronic **decubitus** (pressure sores) and arterial ulcers; and acute wounds.

SUMM [0001] This invention relates to the use of cyclic guanosine 3', 5'-monophosphate type five (cGMP **PDE5**) inhibitors (hereinafter **PDE5** inhibitors), including in particular the compound sildenafil, for the treatment of chronic wounds of a non-diabetic origin including in particular chronic venous ulcers, chronic decubitus (pressure sores) and arterial ulcers; and acute wounds.

SUMM [0009] It is known that cGMP **PDE5** inhibitors increase intracellular concentrations of nitric oxide derived cGMP, thereby enhancing the effect of nitric oxide, which is responsible for the efficacy of sildenafil in the treatment of male erectile dysfunction.

SUMM [0010] We have found elevated levels of the enzyme cGMP **PDE5** in wounded tissue. In particular, where the tissue is inflamed or scarred. Myofibroblasts in healing wounds i.e skin and areas of

organising infarction in, for example, cardiac tissue from patients with ischaemic heart disease express **PDE** 5 whereas fibroblasts populating those areas in non-pathological conditions demonstrate no **PDE** 5 expression. Myofibroblasts from granulation tissue in normally healing wounds temporarily express a smooth muscle phenotype whereas myofibroblasts with a smooth muscle phenotype persist in abnormally healing wounds and fibro-proliferative conditions. cGMP inhibits smooth muscle cell proliferation and thus potentiation of cGMP levels potentially leads to improved wound healing.

SUMM [0011] Without wishing to be bound by theory, it is believed that the wound healing effect is due to improved blood supply to the wound region. **PDE** 5 inhibition at an appropriate stage in the wound-healing cycle in conjunction with an appropriate signal such as NO-mediated smooth muscle relaxation results in vasodilation leading to wound healing. Other factors may also be involved.

SUMM [0013] According to a first aspect, the invention provides a method of treating wounds in a patient which comprises treating the patient with an effective amount of a cGMP **PDE5** inhibitor, or a pharmaceutical composition thereof, wherein the wound type is selected from: chronic venous ulcers, chronic arterial ulcers, chronic decubitus and acute wounds.

SUMM [0014] According to a second aspect, the invention provides the use of a cGMP **PDE5** inhibitor for the manufacture of a medicament for the treatment of wounds, selected from the following types: chronic venous ulcers, chronic arterial ulcers, chronic decubitus and acute wounds.

SUMM [0015] By **PDE5** inhibitors it is meant a compound which is a potent and selective inhibitor of the cGMP **PDE5** isoenzyme.

SUMM [0016] Suitable **PDE5** inhibitors for use in the pharmaceutical combinations according to the present invention are the cGMP **PDE5** inhibitors hereinafter detailed. Particularly preferred for use herein are potent and selective cGMP **PDE5** inhibitors.

SUMM [0017] Suitable cGMP **PDE5** inhibitors for the use according to the present invention include:

SUMM [0035] Still other type CGMP **PDE5** inhibitors useful in conjunction with the present invention include:4-bromo-5-(pyridylmethylamino)-6-[3-(4-chlorophenyl)-propoxy]-3(2H)pyridazinone; 1-[4-[(1,3-benzodioxol-5- ylmethyl)amiono]-6-chloro-2-quinozolinyl]-4-piperidine-carboxylic acid, monosodium salt; (+)-cis-5,6a,7,9,9,9a-hexahydro -2-[4-(trifluoromethyl)-phenylmethyl-5-methyl-cyclopent -4,5]imidazo[2,1-b]purin-4(3H)one; furaziocillin; cis-2-hexyl-5-methyl -3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]-imidazo[2,1 -b]purin-4-one; 3-acetyl- 1-(2-chlorobenzyl)-2-propylindole-6- carboxylate; 3-acetyl-1 -(2-chlorobenzyl)-2-propylindole-6-carboxylate; 4-bromo-5-(3-pyridylmethylamino)-6-(3-(4-chlorophenyl)propoxy)-3- (2H)pyridazinone; I-methyl-5(5-morpholinoacetyl-2-n-propoxyphenyl) -3-n-propyl-1, 6-dihydro-7H-pyrazolo(4, 3-d)pyrimidin-7-one; 1-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-6-chloro-2-quinazolinyl]-4-piperidinecarboxylic acid, monosodium salt; Pharmaprojects No. 4516 (Glaxo Wellcome); Pharmaprojects No. 5051 (Bayer); Pharmaprojects No. 5064 (Kyowa Hakko; see WO 96/26940); Pharmaprojects No. 5069 (Schering Plough); GF-196960 (Glaxo Wellcome); E-8010 and E-4010 (Eisai); Bay-38-3045 & 38-9456 (Bayer) and Sch-51866.

SUMM [0036] According to a third aspect of the invention there is provided a pharmaceutical pack comprising: a pharmaceutical composition comprising a **PDE5** inhibitor, directions relating to the use of the

composition for treating wounds, and a container.

SUMM [0037] For the avoidance of doubt, the **PDE** 5 inhibiting compounds referred to above which are described in detail in the referenced published patent specifications mentioned above specifically form a part of this disclosure and represent a part of the inventive subject matter of this application.

SUMM [0038] The suitability of any particular cGMP **PDE5** inhibitor can be readily determined by evaluation of its potency and selectivity using literature methods followed by evaluation of its toxicity, absorption, metabolism, pharmacokinetics, etc in accordance with standard pharmaceutical practice.

SUMM [0039] Preferably, the cGMP **PDE5** inhibitors have an IC50 for **PDE5** at less than 100 nanomolar, more preferably, at less than 50 nanomolar, more preferably still at less than 10 nanomolar.

SUMM [0040] IC50 values for the cGMP **PDE5** inhibitors may be determined using established literature methodology, for example as described in EP0463756-B1 and EP0526004-A1.

SUMM [0041] Preferably the cGMP **PDE5** inhibitors used in the invention are selective for the **PDE5** enzyme. Preferably they are selective over **PDE3**, more preferably over **PDE3** and **PDE4**. Preferably, the cGMP **PDE5** inhibitors of the invention have a selectivity ratio greater than 100 more preferably greater than 300, over **PDE3** and more preferably over **PDE3** and **PDE4**.

SUMM [0042] Selectivity ratios may readily be determined by the skilled person. IC50 values for the **PDE3** and **PDE4** enzyme may be determined using established literature methodology, see S A Ballard et al, Journal of Urology, 1998, vol. 159, pages 2164-2171.

SUMM [0048] Preferably the cGMP **PDE5** inhibitor is Sildenafil.

SUMM [0049] The cGMP **PDE5** inhibitors can be administered alone but, in human therapy will generally be administered in admixture with a suitable pharmaceutical excipient diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

SUMM [0050] For example, the cGMP **PDE5** inhibitors can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, or controlled-release applications.

SUMM [0052] Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the cGMP **PDE5** inhibitors of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

SUMM [0053] The cGMP **PDE5** inhibitors can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intramuscularly or subcutaneously, or they may be administered by infusion techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make

the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

SUMM [0055] The dosage of cGMP **PDE5** inhibitor in such formulations will depend on its potency, but can be expected to be in the range of from 1 to 500 mg for administration up to three times a day. For oral and parenteral administration to human patients, the daily dosage level of the cGMP **PDE5** inhibitor will usually be from 5 to 500 mg (in single or divided doses). In the case of sildenafil, a preferred dose is in the range 10 to 100 mg (e.g. 10, 25, 50 and 100 mg) which can be administered once, twice or three times a day (preferably once). However the precise dose will be as determined by the prescribing physician and will depend on the age and weight of the patient and severity of the symptoms.

SUMM [0056] Thus, for example, tablets or capsules of the cGMP **PDE5** inhibitor may contain from 5 to 250 mg (e.g. 10 to 100 mg) of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

SUMM [0057] The cGMP **PDE5** inhibitors can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebuliser with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of the cGMP **PDE5** inhibitor, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of the cGMP **PDE5** inhibitor and a suitable powder base such as lactose or starch.

SUMM [0058] Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 50 mg of the cGMP **PDE5** inhibitor, for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 to 50 mg which may be administered in a single dose or, more usually, in divided doses throughout the day. Alternatively, the cGMP **PDE5** inhibitors can be administered in the form of a suppository or pessary.

SUMM [0059] The cGMP **PDE5** inhibitor may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The cGMP **PDE5** inhibitors may also be dermally or transdermally administered, for example, by the use of a skin patch.

SUMM [0061] For application topically to the skin, the cGMP **PDE5** inhibitors can be formulated as a suitable ointment containing the inhibitor suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying

wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

SUMM [0062] The cGMP **PDE5** inhibitors may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drugcyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A98/55148.

SUMM [0063] Generally, in humans, oral administration of the cGMP **PDE5** inhibitors is the preferred route, being the most convenient. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, sublingually or buccally.

SUMM [0064] The cGMP **PDE5** inhibitors of the invention can also be administered in combination with one or more of the following:

SUMM [0072] viii) Matrix metalloprotease inhibitors (**MMP**), particularly **MMP**-3, **MMP**-12 and **MMP**-13; and

SUMM [0074] Particularly preferred agents for use in combination with the **PDE5** inhibitors of the invention for treating wounds include: **MMP** inhibitors (particularly inhibitors of **MMP**-3, **MMP**-12 and **MMP**-13); uPA inhibitors; and vasodilator agents (particularly pentoxyfyline).

SUMM [0075] Preferably the **MMP** inhibitor is a **MMP**-3 and/or **MMP**-13 inhibitor such as those specifically and generically disclosed in WO99/35124, EP 931788, WO99/29667 or WO00/74681. Especially preferred **MMP** inhibitors are those of the Examples of WO099/35124, EP 931788, WO99/29667 and WO00/74681.

DETD [0085] Anti-human polyclonal antiserum was raised in rabbits and affinity purified against the LIP-1 [MERAGPSFGQQR] peptide n accordance with the method of Fawcett et al (Proc Natl Acod Sci USA 2000; 97:3702-3707), corresponding to amino acid residues 1-12 of human **PDE5A1**. LIP-1 is specific for **PDE5** A1.

DETD [0088] FIG. 1 illustrates a section of reactive but non-inflamed skin at the edge of a skin wound. The positive staining of the smooth muscle cells within the media of the venules and negative fibroblasts indicates the expression of **PDE5** in the healing wound. Hyperplastic but intact squamous epithelium 1 is negative. The underlying dermis contains mature scar tissue with small and large venules 2. Note the positive dark staining of the smooth muscle cells within the media of the venules (Original mag. .times.10).

DETD [0089] FIG. 2 is a paraffin section taken from the border between a healing ulcer of 14 days (left) and intact epithelium (right). Again, the positive staining of the smooth muscle cells within the media of the venules (right) and the spindle cells (myofibroblasts) within the base of the ulcer (left) indicates **PDE5** expression. Hyperplastic but intact squamous epithelium (right) and necrotic inflammatory exudate 3 is negative. Note the positive dark staining of the smooth muscle cells within the media of the venules 4 and of spindle cells within the

base of the ulcer 5 (original mag. .times.20).

DETD [0090] FIG. 3 is a paraffin section taken from the healed ulcer base w her e fascicles of young scar tissue have replaced normal dermal structures. Positive staining of some of the spindle cells (myofibroblasts) (8) and of some vascular structures is again indicative of **PDE** 5 expression. (Original mag .times.20).

DETD [0091] FIG. 4 is a higher power view of the paraffin section of skin of FIG. 3. The section is taken from the healed ulcer base where fascicles of young scar tissue have replaced normal dermal structures. **PDE** 5 expression is illustrated by the positive staining of some of the spindle cells (myofibroblasts) (9) and of some of the microvessels which have thin media (10). (Original mag x40).

DETD [0092] FIG. 5 is a higher powered view of FIG. 4 and shows a section taken from the healed ulcer base of FIG. 4 where fascicles of young scar tissue have replaced normal dermal structures. There is positive staining of some of the spindle cells (myofibroblasts) (11) which are present in acellular collagen. The immunolocalisation in the cytoplasm of some of these spindle cells has a patchy distribution. Positive staining of the medial smooth muscle cells within a small arteriole (12) indicates **PDE** 5 expression. There is negative staining of the lining endothelial cells (13) indicating the absence of **PDE** 5. (Original mag. .times.60).

DETD [0093] FIG. 6 is also a higher powered view of FIG. 4 showing a section from the healed ulcer base in an area of relatively young scar tissue. Again, positive staining of some of the spindle cells (myofibroblasts) (14) and medial smooth muscle cells within the small arteriole (centre) (15) is indicative of **PDE** 5. In some of these spindle cells the immunolocalisation has a patchy distribution. (Original mag. .times.60).

DETD [0094] The following formulation examples are illustrative only and are not intended to limit the scope of the invention. Active ingredient means a cGMP **PDE5** inhibitor.

CLM What is claimed is:

1. A method of treating wounds in a patient which comprises treating the patient with an effective amount of a cGMP **PDE5** inhibitor, or a pharmaceutical composition thereof, wherein the wound type is selected from: chronic **venous ulcers**, chronic arterial ulcers, chronic **decubitus** and acute wounds:

2. The use of a cGMP **PDE5** inhibitor for the manufacture of a medicament for the treatment of wounds, selected from the following types: chronic **venous ulcers**, chronic arterial ulcers, chronic **decubitus** and acute wounds.

9. The use of a cGMP **PDE5** inhibitor in combination with a matrix metalloprotease inhibitor (**MMP**), and/or a urokinase type plasminogen activator inhibitor (uPA), for the manufacture of a medicament for the treatment of wounds, selected from the following types: chronic **venous ulcers**, chronic arterial ulcers, chronic **decubitus** and acute wounds.

10. Use as claimed in claim 9, wherein the **MMP** is selected from the group comprising: inhibitors of **MMP**-3, **MMP**-12 and **MMP**-13.

11. A pharmaceutical pack comprising: a pharmaceutical composition comprising a **PDE5** inhibitor, directions relating to the use of the composition for treating wounds, and a container.

12. A combination of a **PDE5** inhibitor together with a matrix metalloprotease inhibitor (**MMP**) and/or a urokinase type plasminogen activator inhibitor (uPA).

13. A combination as claimed in claim 12, wherein the **MMP** is

selected from the group comprising: inhibitors of **MMP**-3, **MMP**-12 and **MMP**-13.

L8 ANSWER 2 OF 3 USPATFULL

ACCESSION NUMBER:	2000:174710 USPATFULL		
TITLE:	Compositions for the treatment of chronic wounds		
INVENTOR(S):	Bloor, Stephen, Preston, United Kingdom		
PATENT ASSIGNEE(S):	Johnson & Johnson Medical, Ltd., Edinburgh, United Kingdom (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6166084		20001226
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PRIMARY EXAMINER:	Cook, Rebecca		
LEGAL REPRESENTATIVE:	Farmer, Andrew C., Shatynski, Theodore J.		
NUMBER OF CLAIMS:	20		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)		
LINE COUNT:	464		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides the use of N-acetyl cysteine and its pharmaceutically acceptable salts and derivatives, for the preparation of a composition for treatment or prophylaxis of chronic ulcers. In particular, the treatment of **venous ulcers**, diabetic ulcers and **decubitis** ulcers.

SUMM Without wishing to be bound by any theory, it is thought that the NAC promotes healing or prophylaxis of chronic ulcers by regulating matrix metalloproteinases (**MMP**'s) at the ulcer site. It is thought that the balance between proteolytic enzymes and their inhibitors is critical to the persistence and healing of chronic ulcers, and that the NAC corrects this balance in chronic ulcers.

SUMM In addition, the NAC may influence chronic ulcers through the following mechanisms. Firstly, by inhibition of tumour necrosis factor (TNF) mediated effects. NAC has the potential to inhibit the effects of TNF by interfering with the intracellular signalling resulting from the TNF receptor activation. Secondly, NAC can also neutralise potentially harmful oxygen radicals, which in turn can induce the expression of **MMP**'s and other molecules. Thirdly, NAC has the potential to inhibit the influx of inflammatory cells to a wound site by inhibiting the transcription of genes for adhesion molecules such as ICAM-1 and other adhesion molecules on inflammatory cells and endothelial cells. It can do this by inhibiting the activation of nuclear transcription factors such as NF.sub.k -B, which controls the transcription of the **MMP**-9 gene, adhesion molecule genes such as ICAM-1 and inflammatory mediator genes such as TNF-.alpha.. Finally, NAC can interfere with the inflammatory mediators such as leukotrienes.

DRWD FIG. 2 shows a bar chart of matrix metalloproteinase (**MMP**) activity in arbitrary units in the presence of 0 (control), 0.4 mM, 4.4 mM and 44 mM concentration of NAC.

DETD The effect of NAC concentration on the activity of matrix metalloproteinases (**MMP**) from human wound fluid was assessed as follows.

DETD The **MMP** activity was determined by gelatin SDS polyacrylamide gel electrophoresis (zymography) similar to that described by Heussen C.

and Dowdle E. B. in Anal. Biochem. 102:196-202 (1980).

DETD 2. Sample preparation: A matrix metalloprotease (**MMP**) sample (10% solution of human acute wound fluid diluted in **MMP** proteolysis buffer (see below)) was diluted 1:1 with sample buffer (6.3 ml 0.5M Tris-HCl pH 6.8, 2.5 ml glycerol, 0.5 g SDS, 16.2 ml deionised water and bromophenol blue to colour).

DETD 3. Sample loading and electrophoresis: 20 .mu.l of the **MMP** samples were loaded into 8 lanes of the gel. The **MMP**'s were separated for 1 hour at 20 mA/100V per gel until the dye front was almost at the bottom of the gel. The gel apparatus was then dismantled and the gel removed.

DETD 5. Gel development: The gels were washed with deionised water and stained with 0.1% Coomassie blue R250 in 10% acetic acid, 40% methanol and 50% delonised water for 1 hour. The gels were then destained with 7.5% acetic acid, 10% methanol and 82.5% deionised water until zones of proteolysis had resolved in the controls (**MMP** sample incubated in proteolysis buffer alone).

DETD The results, shown in FIG. 2, demonstrate a clear concentration-dependent inhibition of **MMP** activity with NAC concentration. The inhibition of **MMP** activity is substantially complete in 44 mM NAC solution. Approximately 70% inhibition is observed in 4.4 mM NAC solution, and approximately 10% inhibition in 0.44 mM NAC.

CLM What is claimed is:

1. A method for the treatment or prophylaxis of a chronic wound in a mammal, the chronic wound being selected from the group consisting of **venous ulcers**, diabetic ulcers, and pressure sores, the method comprising the step of topically applying to the chronic wound an effective amount of a composition comprising a compound of the formula: ##STR2## wherein: R.sub.1 is H, C.sub.1 -C.sub.10 alkyl, C.sub.6 -C.sub.14 aryl, or an inorganic, alkyl ammonium or protonated amino acid cation; R.sub.2 is H, C.sub.1 -C.sub.10 alkyl, C.sub.6 -C.sub.14, aryl optionally substituted --C O C.sub.6 -C.sub.14 alkyl, optionally substituted --C S C.sub.6 -C.sub.14 alkyl, optionally substituted --C O C.sub.6 -C.sub.14 aryl, optionally substituted --C S C.sub.6 -C.sub.14 aryl, or R.sub.2 together with the sulfur to which it is attached form a thioester of a saturated or unsaturated fatty acid, lactic acid, retinoic acid or ascorbic acid; and R.sub.3 is H, C.sub.1 -C.sub.10 alkyl or C.sub.6 -C.sub.14 aryl; or a pharmaceutically acceptable salt thereof; thereby inhibiting matrix metalloproteinases in said chronic wound.

2. A method for the treatment or prophylaxis of a chronic wound in a mammal, the chronic wound being selected from the group consisting of **venous ulcers**, diabetic ulcers, and pressure sores, the method comprising the step of systemically administering an effective amount of a composition comprising a compound of the formula: ##STR3## wherein: R.sub.1 is H, C.sub.1 -C.sub.10 alkyl, C.sub.6 -C.sub.14 aryl, or an inorganic, alkyl ammonium or protonated amino acid cation; R.sub.2 is H, C.sub.1 -C.sub.10 alkyl, C.sub.6 -C.sub.14 aryl, optionally substituted --C O C.sub.6 -C.sub.14 alkyl, optionally substituted --C S C.sub.6 -C.sub.14 alkyl, optionally substituted --C O C.sub.6 -C.sub.14 aryl, optionally substituted --C S C.sub.6 -C.sub.14 aryl, or R.sub.2 together with the sulfur to which it is attached form a thioester of a saturated or unsaturated fatty acid, lactic acid, retinoic acid or ascorbic acid; and R.sub.3 is H, C.sub.1 -C.sub.10 alkyl or C.sub.6 -C.sub.14 aryl; or a pharmaceutically acceptable salt thereof; thereby inhibiting matrix metalloproteinases in said chronic wound.

6. A method for the treatment or prophylaxis of a chronic wound in a mammal, the chronic wound being selected from the group consisting of **venous ulcers**, diabetic ulcers, and pressure sores, the method comprising the step of topically applying to the chronic wound an effective amount of a composition comprising gluthathione or a

pharmaceutically acceptable salt thereof, thereby inhibiting matrix metalloproteinases in said chronic wound.

7. A method for the treatment or prophylaxis of a chronic wound in mammals, the chronic wound being selected from the group consisting of **venous ulcers**, diabetic ulcers, and pressure sores,
the method comprising the step of systemically administering an effective amount of a composition comprising gluthathione or a pharmaceutically acceptable salt thereof, thereby inhibiting matrix metalloproteinases in said chronic wound.

11. A method for inhibiting matrix metalloproteinases for the treatment or prophylaxis of a chronic wound in a mammal, the chronic wound being selected from the group consisting of **venous ulcers**,
diabetic ulcers, and pressure sores, the method comprising the step of topically applying to the chronic wound an effective amount of a composition comprising a compound of the formula: ##STR4## wherein: R.sub.1 is H, C.sub.1 -C.sub.10 alkyl, C.sub.6 -C.sub.14 aryl, or an inorganic, alkyl ammonium or protonated amino acid cation; R.sub.2 is H, C.sub.1 -C.sub.10 alkyl, C.sub.6 -C.sub.14 aryl, optionally substituted --C O C.sub.6 -C.sub.14 alkyl, optionally substituted --C S C.sub.6 -C.sub.14 alkyl, optionally substituted --C O C.sub.6 -C.sub.14 aryl, optionally substituted --C S C.sub.6 -C.sub.14 aryl, or R.sub.2 together with the sulfur to which it is attached form a thioester of a saturated or unsaturated fatty acid, lactic acid, retinoic acid or ascorbic acid; and R.sub.3 is H, C.sub.1 -C.sub.10 alkyl or C.sub.6 -C.sub.14 aryl; or a pharmaceutically acceptable salt thereof; thereby inhibiting said matrix metalloproteinases in said chronic wound.

12. A method for inhibiting matrix metalloproteinases for the treatment or prophylaxis of a chronic wound in a mammal, the chronic wound being selected from the group consisting of **venous ulcers**,
diabetic ulcers, and pressure sores, the method comprising the step of systemically administering an effective amount of a composition comprising a compound of the formula: ##STR5## wherein: R.sub.1 is H, C.sub.1 -C.sub.10 alkyl, C.sub.6 -C.sub.14 aryl, or an inorganic, alkyl ammonium or protonated amino acid cation; R.sub.2 is H, C.sub.1 -C.sub.10 alkyl, C.sub.6 -C.sub.14 aryl, optionally substituted --C O C.sub.6 -C.sub.14 alkyl, optionally substituted --C S C.sub.6 -C.sub.14 alkyl, optionally substituted --C O C.sub.6 -C.sub.14 aryl, optionally substituted --C S C.sub.6 -C.sub.14 aryl, or R.sub.2 together with the sulfur to which it is attached form a thioester of a saturated or unsaturated fatty acid, lactic acid, retinoic acid or ascorbic acid; and R.sub.3 is H, C.sub.1 -C.sub.10 alkyl or C.sub.6 -C.sub.14 aryl; or a pharmaceutically acceptable salt thereof; thereby inhibiting said matrix metalloproteinases in said chronic wound.

16. A method for inhibiting matrix metalloproteinases for the treatment or prophylaxis of a chronic wound in a mammal, the chronic wound being selected from the group consisting of **venous ulcers**,
diabetic ulcers, and pressure sores, the method comprising the step of topically applying to the chronic wound an effective amount of a composition comprising gluthathione or a pharmaceutically acceptable salt thereof, thereby inhibiting said matrix metalloproteinases in said chronic wound.

17. A method for inhibiting matrix metalloproteinases for the treatment or prophylaxis of a chronic wound in mammals, the chronic wound being selected from the group consisting of **venous ulcers**,
diabetic ulcers, and pressure sores, the method comprising the step of systemically administering an effective amount of a composition comprising gluthathione or a pharmaceutically acceptable salt thereof, thereby inhibiting said matrix metalloproteinases in said chronic wound.